Letters to the Editors

Effect of a single oral dose of Fansidar™ on the pharmacokinetics of halofantrine in healthy volunteers: a preliminary report

In many countries multidrug resistant *Plasmodium falciparum* malaria is an increasing problem [1]. Halofantrine is a recent addition to the therapeutic arsenal [2] and it has already earned an important place in the treatment of uncomplicated, multidrug resistant disease [3]. However, in some countries there are reports of resistance to halofantrine [4, 5]. To prevent its further spread and to delay the onset of resistance to this new drug in areas not experiencing resistance, it would seem appropriate to recommend that halofantrine be used in combination with other antimalarial drugs. Halofantrine and sulphadoxine-pyrimethamine (Fansidar™) is one option. If so, assessing the clinical and pharmacokinetic profiles of this combination becomes mandatory for rational utilization of the drugs. This study examined the effect of Fansidar™ on single-dose halofantrine pharmacokinetics in healthy Papua New Guinean volunteers.

Seven healthy male subjects (18–40 years; 45–70 kg), none of whom was on regular medication, volunteered to take part in the study. Each volunteer gave informed consent to participate in the study that was approved by the Ethics and Medical Research Committee of the Faculty of Medicine, University of Papua New Guinea. One day before drug administration, each subject had a physical examination, routine laboratory (haematologic and biochemical) investigations, excepting ECG tracings. The subjects were randomized to receive either halofantrine alone or halofantrine and Fansidar™ (sulphadoxine-500 mg, pyrimethamine 25 mg) in a simple crossover, two phased study design with an interval of not less than 4 weeks between treatments. On the first occasion, after an overnight fast, the subjects were randomized to receive halofantrine or coadministration of halofantrine and Fansidar. Fansidar™; (2 tablets) was given orally 15 min prior to a single dose of halofantrine (250 mg tablet × 2). Excepting for fluids, solids were not permitted until 2 h postdosing, and all drugs were coadministered with water (∼100 ml). Whole blood samples (5 ml) were collected into heparinized tubes at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8,12, and 24 h and on days 2, 3, 4, 5, 7, 14 and 28. Any adverse events were recorded especially gastrointestinal, central nervous system, cardiovascular, and dermatological and any other complaints possibly attributable to halofantrine. Plasma was separated and stored at −80° C until analysis within 6 months. Plasma concentrations of halofantrine and *N*-desbutylhalofantrine were determined by reverse-phase automated high performance liquid chromatography with Photodiode Array detection after direct liquid-phase extraction as described previously [6]. An on-line computer software program (Millennium, Waters™) was used to generate standard curves for halofantrine and desbutylhalofantrine from which, respective drug concentrations were calculated and read automatically. The internal standard was 2,4-dichloro-6-trifluoro-9-(2-dibutylamino) ethyl. Smith Kline-Beecham laboratories provided halofantrine, *N*-desbutylhalofantrine, and internal standard. Accuracy of the assay was calculated as the percentage difference between the known concentration in spiked samples and concentration measured in the assay. The intra-and interassay (between days) precision of the method (<10% for each analyte) was determined by assaying replicates ($n = 8$) of spiked samples at range of the drug concentrations (25, 50, 100, 250, 500, 1000 ng ml^{-1}) for halofantrine and its metabolite. The practical limit of detection in this system (15 ng ml^{-1} for each analyte) was defined as the minimum concentration detectable with a signal to noise ratio of 3 : 1. The peak plasma concentration (C_{max}) and time to reach peak concentration (t_{max}) were noted directly from the log concentration *vs* time profiles. Other pharmacokinetic parameters were calculated by using standard noncompartmental methods [7] using the pharmacokinetic program package KINETICA™, version 2.0.2 (INNAPHASE, France). The absorption half-life ($t_{½,abs}$) was calculated by Wagner-Nelson modified method in the program package. Data were expressed as arithmetic means with 95% confidence intervals. All statistical calculations were carried out by the SigmaStat® program package, version 2.01 (Jandel Corporation, USA). The pharmaco-kinetic parameters for two drug schedules were compared with the use of the Student's paired *t*-test. *P* values of less than 0.05 were regarded as statistically significant., No significant drug related adverse events were reported and the results of laboratory investigations were uneventful. The pharmacokinetic variables for halofantrine alone and coadministration with Fansidar™ are summarized in Table 1. In the presence of Fansidar™ increases were observed with halofantrine AUC(0,6 h) ($P < 0.05$) and the C_{max} ($P > 0.05$). However, absorption half-life ($t_{½,abs}$), terminal half-life ($t_{½,z}$), total AUC(0,∞), and t_{max} values were similar on both occasions. Thus the data suggest that Fansidar™ increased the extent but not the rate of oral halofantrine absorption.

These observations might indicate increases in peak plasma concentrations during multiple dose administration. Obviously, this would lead to relatively greater

Table 1 Pharmacokinetic parameters (arithmetic mean, 95% confidence interval) of halofantrine and desbutylhalofantrine in the presence or absence of Fansidar™; in seven healthy volunteers after a single oral dose administration of halofantrine HCl.

Parameters	*Halofantrine only*	*Halofantrine/ Fansidar™*	*Difference of mean (95% confidence interval)*
Halofantrine			
C_{max} (ng ml $^{-1}$)	89.2	138.9	49.7
	(50.1, 128.3)	(98.3, 179.6)	(−5.5, 105.0)
t_{max} (h)	4.9	4.6	0.3
	(3.4, 6.4)	(3.3, 5.9)	(−1.5, 2.0)
$t_{1/2,z}$ (h)	27.8	26.7	1.6
	(21.7, 33.8)	(15.7, 37.9)	(−8.9, 12.1)
$t_{1/2,abs}$ (h)	1.9	1. 2	0.7
	(1.0, 2.8)	(1.0, 1.5)	(−0.34, 1.91)
AUC(0,6 h)	290.8	498.8	208.1*
(ng ml $^{-1}$ h)	(167.3, 414.3)	(378.0, 619.6)	(24.3, 391.9)
AUC(0,∞)	3043.7	2730.2	484.0
(ng ml $^{-1}$ h)	(288.4, 5799.0)	(1992.2, 3541.2)	(−2567.0, 3536.6)
Desbutylhalofantrine			
C_{max} (ng ml $^{-1}$)	48.3	64.1	15.8
	(27.7, 69.1)	(39.2, 89.0)	(−13.1, 44.7)
t_{max} (h)	10.0	8.0	2.0
	(3.9, 16.1)	(5.1, 10.9)	(−4.0, 8.0)
$t_{1/2,z}$ (h)	53.9	40.5	13.4
	(37.2, 70.6)	(22.3, 58.6)	(−12.5, 39.3)
AUC(0,6 h)	118.2	211.4	93.2*
(ng ml $^{-1}$ h)	(42.1, 194.3)	(99.7, 323.0)	(13.8, 172.6)
AUC(0,∞)	2807.3	2962.7	155.3
(ng ml $^{-1}$ h)	(1422.2, 4192.1)	(2131.6, 3793.7)	(−1598.4, 3507.1)

*Statistically significant ($P < 0.05$).

plasma concentration of halofantrine; a factor that might contribute to cardiotoxicity should halofantrine be used in combination with Fansidar™ for malaria treatment. Although electrocardiograms (ECG) were not done, minimal ECG changes with lengthening of QT interval without clinical symptoms are frequent and these changes, at least in ECG terms, are dose/concentration-dependent [8]. Therefore, it is one of the manufacturers recommendations that halofantrine should not be used in combination with drugs that prolong QT interval or in clinical situations likely to do so.

The increases in the halofantrine C_{max} and AUC(0,6 h) values, obtained in the presence of a single dose of Fansidar™ appear not to cause any obvious clinical toxicity. The mechanism underlying such increases is unclear, but a possibility of enhanced halofantrine absorption following prior oral intake of Fansidar™ cannot be excluded and needs further investigation.

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Genetic polymorphism of CYP2D6 in a Keralite (South India) population

CYP2D6, which exhibits genetic polymorphism, is involved in the metabolism of more than 40 drugs especially neuroleptics, antidepressants, certain anti-arrhythmics and lipophilic β-adrenergic receptor blockers as well as opioids such as codeine [1]. Pronounced interethnic differences in the prevalence of this polymorphism are known to exist. The poor metaboliser (PM) phenotype is present in, for example, 5–10% of European-derived Caucasians [2], less than 1% of Chinese [3] and Japanese [4], 1% of Saudi Arabians [5], 0–2% of black populations [2] 1.2% of Thais [6] and 0–2% of Sinhalese in Sri Lanka [7]. However, the CYP2D6 polymorphism in Indian populations has not been studied extensively. A study among subjects resident in Bombay, which is on the west coast of the central part of India, reported 2% PM with respect to CYP2D6 [8]. A much more recent study shows a frequency of 3% PM in a North Indian population [9]. Since CYP2D6 polymorphism has not been studied in a Keralite population, the present study was undertaken. Kerala is a small state, on the west coast of South India. The nontribal population of Kerala consists of Caucasoid Dravidians, whereas those of Bombay, North India and Sinhalese in Sri Lanka are Caucasoid Aryans [10].

The study was performed in 104 volunteers residing in Kerala, who were mostly students and staff from Mahatma Gandhi University, Kottayam, Kerala. Sixty-four were males and 39 were females in the age range of 17–44 years (mean $\pm$ s.d. age, 23.5 $\pm$ 3.7 years). The mean body mass index $\pm$ s.d. was 20.7 $\pm$ 2.6. All subjects gave their informed consent and the study was approved by the Ethics committee, JIPMER, Pondicherry. All subjects were judged to be in good health as determined by a medical history, physical examination and blood pressure measurement. They were on no medication and drank no alcohol for at least 2 weeks before the study.

After voiding their bladder prior to bedtime, participants ingested 30 mg dextromethorphan (5 ml of Lactuss-LA, cough suspension: FDC Limited, Aurangabad, India). Urine was collected overnight for 8 h. A 20 ml aliquot was stored at –20° C until analysis for dextromethorphan (DM) and dextrorphan (DT) by h.p.l.c [11]. The inter and intraday coefficient of variation for assay of DM and DT (50–8000 ng ml^{-1}) were less than 10% and 5%, respectively. The least quantifiable amount was 20 ng ml^{-1} for both DM and DT.

The oxidative phenotype assignment was based on the value of the molar urinary ratio of DM to DT (metabolic ratio) in relation to the population antimode. Subjects with a metabolic ratio greater than 0.3 were classified as poor metabolisers with respect to the CYP2D6 enzyme [12].

Ninety-six subjects (92.62%) had metabolic ratios between 0.005 and 0.192 and were classified as extensive metabolisers (EM). Five subjects were identified as PM: four males and one female. They had metabolic ratios between 0.315 and 3.14 (Figure 1). This corresponds to a prevalence of the PM phenotype of 4.8% with a 95% confidence interval of 1.6–10.9%. Three subjects (two males and one female) who had very low metabolic ratios between 0.0034 and 0.0039 may be identified as ultra extensive metabolisers (UEM) with very high enzyme activity [1].

The distribution of the metabolic ratio was not significantly different between male and female subjects ($P > 0.05$). No side-effects or any adverse drug reactions were observed. The body mass index of the subjects did not significantly influence the metabolic ratio ($P > 0.05$).

The prevalence of PM in the Keralite population is more than the mean value of approximately 1% observed in other Asian populations [3–7]. The metabolic ratio is determined by factors such as renal drug clearance as well as enzyme activity. Environmental factors may modify these variables which may give rise to differences in the antimode of the metabolic ratio between ethnic groups [6]. However the prevalence of PM with respect to CYP2D6 in the Dravidian population of Kerala differs from that reported in the Indo-Aryan subjects of Sri Lanka, Bombay and North India (0–3%) [7–9].

There is a rightward shift in the frequency distribution curve of dextromethorphan in the Keralite population compared with the Caucasian population studied by Christian *et al.* ($P < 0.001$) [13]. However the frequency distribution pattern of the Keralite population is comparable with that reported in a North Indian population ($P > 0.05$) [9]. A similar interethnic difference in the frequency distribution of the metoprolol metabolic ratio has also been observed between Chinese and Japanese populations [14]. Differences between white subjects and subjects from Kerala in lifestyle, dietary habits, and/or occupation may contribute to this ethnic difference in the activity of CYP2D6.

This is the first study of the pattern of CYP2D6 enzyme activity in the Keralite population. Since this ethnic group has migrated widely to different parts of the world, these results may serve as a basis for further studies to test the relationship between drug oxidation polymorphism and drug induced adverse reactions or diseases of unknown aetiology in Keralites. Further study in other South Indian states can give a clearer picture of the CYP2D6 polymorphism in this region.

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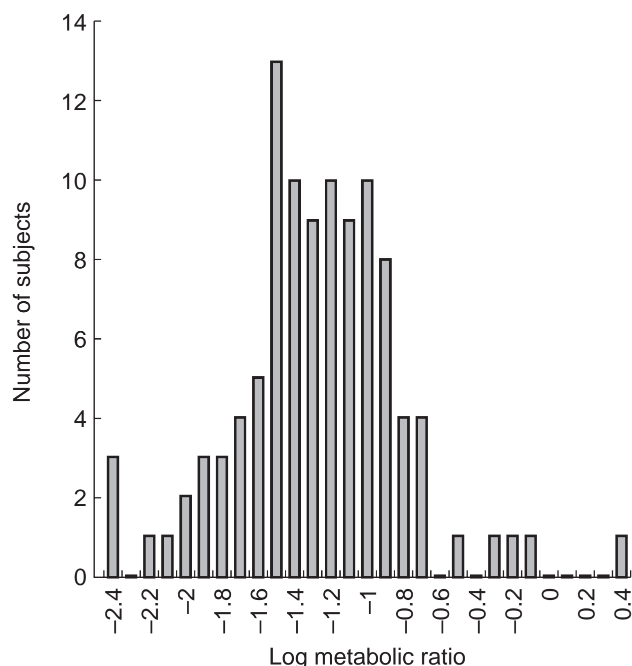

Figure 1 Distribution of the dextromethorphan metabolic ratio among 104 keralite subjects.

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Excretion of fluvoxamine into breast milk

Treatment with antidepressants is regularly demanded in post partum women due to the high prevalence of mood and anxiety disorders during this period. In general treatment with selective serotonin reuptake inhibitors (SSRIs) have been considered to be compatible with breast-feeding [1, 2] although some concern has been alleged about the use of fluoxetine because of three reports of possible adverse effects in suckling infants whose mothers were treated with fluoxetine [3–5].

The subject of this report is a 31-year old woman with a history of panic disorder but no somatic disease as assessed by medical history, physical examination and routine blood chemistry. Height and body weight were 1.75 m and 90 kg, respectively. The study was performed 3 months post partum. She had then been treated with fluvoxamine for 6 months and for 1 week with the present dosage, 100 mg twice daily. After intake of 100 mg fluvoxamine (Fevarin, enteric-coated fluvoxamine maleate, Solvay Pharma, Brussels, Belgium) at 08.00 h venous blood samples (10 ml) and milk samples (5 ml) from both breasts were collected every hour during a 12 h period.

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Fore milk samples were obtained using a manual breast pump. The first 2 ml of the breast milk was discarded. All milk and serum samples were stored at –20° C until analysis with a previously described high performance liquid chromatography technique [6]. The limit of quantification was 100 nmol l^{-1} and 50 nmol l^{-1} for serum and breast milk, respectively, and the method was linear up to at least 3000 nmol l^{-1} and 1500 nmol l^{-1} for analysis in serum and breast milk, respectively. The intra-assay coefficients of variations for fluvoxamine were 3.1% in serum at 500 nmol $l^{-1}$and 2.1% in milk at 500 nmol l^{-1}.

The following equation was used in order to calculate the absolute daily dose of fluvoxamine ingested by the newborn per kg body weight: $D_{inf} = {}'C_{ss(milk)} \times V_{milk}$ where $'C_{ss(milk)}$ is the average steady state concentration in milk and V_{milk} is the daily volume of milk ingested by the newborn, which was assumed to be 0.15 l kg^{-1} body weight. $'C_{ss(milk)}$ was calculated as the area under the concentration curve (AUC)/12 h. AUC was calculated by using a noncompartment model in the pharmacokinetic program package WinNonlin, version 1.1 (Scientific Consulting Inc., North Carolina, USA). The relative daily fluvoxamine dose ingested by the newborn (D_{rel}) was calculated using the equation: $D_{rel} = D_{inf}/D_{mat} \times 100$ where D_{mat} is the maternal daily fluvoxamine dose kg^{-1} body weight.

Concentrations of fluvoxamine in serum and milk are presented in Figure 1. The time course of fluvoxamine in milk roughly paralleled the serum time profile. Mean of right and left breast milk to serum concentration at each time point ranged between 1.06 and 1.59. The overall milk to serum concentration ratio based on AUC values was 1.32. The absolute daily dose of fluvoxamine ingested by the newborn was calculated to be 48 μg kg^{-1} and the relative dose was calculated to be 1.58% of the weight-adjusted maternal dose.

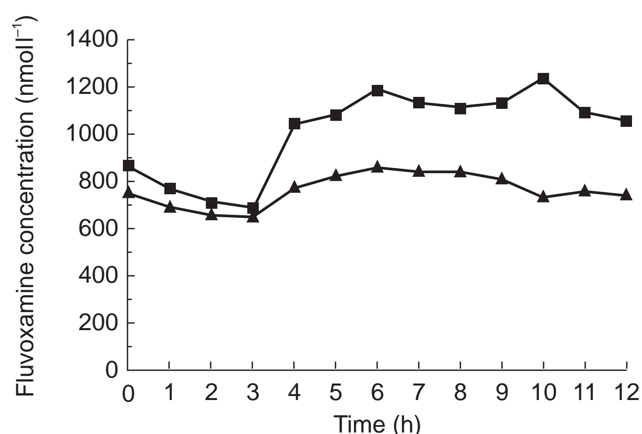

Figure 1 Concentration-time profile in milk (■) and serum (▲) during a dose interval of 12 h at steady state in a subject treated with fluvoxamine 100 mg twice daily. The milk concentrations are average values from the milk samples from both breasts.

Excretion of fluvoxamine in human breast milk has only been documented in two cases before and was based on single pairs of samples only. In these cases milk/plasma ratios were considerably less, 0.29 [7, 8], than the ratio in this woman, which was 1.32. The discrepancy between these figures might be explained at least in part by interindividual differences in lipid contents and pH of the milk. Also, if only fore milk samples are being used a lower concentration will be present. However, in this study even higher milk concentrations of fluvoxamine might have been measured if also hind milk had been used since lipid soluble drugs such as fluvoxamine tend to concentrate in hind milk, which contains more fat than fore milk. Thus, using hind milk in this study would probably have resulted in an even higher M/P-ratio and estimate of the relative weight adjusted dose to the infant. Moreover, by using single pairs of samples the result will be less robust compared to studies with the design used in this study.

Although no correlation between fluvoxamine clearance and systemic caffeine clearance was found in one study [9] the enzyme CYP1A2 has been proposed to be the major enzyme responsible for the metabolism of fluvoxamine [10]. This enzyme is not mature until 4 months of age [11] and in newborns even a low exposure of CYP1A2 substrate might therefore constitute a possible risk for adverse drug reactions. Due to ethical reasons we did not obtain blood samples in this infant, but no adverse drug reaction or unusual behaviour were observed, as was reported for the two previously exposed infants [7, 8].

This study indicates that the relative dose of fluvoxamine to the suckling infant is low, but higher than previously calculated values for fluvoxamine [2]. Moreover, the estimated relative dose is close to the values reported for other SSRIs such as sertraline [2, 12, 13], and paroxetine [2, 14, 15], but somewhat less than values reported for fluoxetine [2, 5, 16] and citalopram [2]. Based on the findings in this case and two others [6, 7] treatment with fluvoxamine seems compatible with breastfeeding. This statement should, however, be regarded as preliminary due to insufficient information about the possible clinical effects from the rather small doses to the suckling infant through breast-feeding.

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