Eur J Clin Pharmacol (1992) 42: 559–560

European Journal of Clinical Pharmacology

Letters to the editors

Pharmacokinetics of mefloquine in the presence of primaquine

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Received: April 16, 1991/Accepted in revised form: September 18, 1991

Key words: Mefloquine, Thai subjects; pharmacokinetics, Primaquine, drug interaction, adverse effects

In the chemotherapy of malaria the achievement of radical treatment requires antimalarial drugs that act on various stages of the parasite cycle. As there is no single drug which can affect radical treatment, a combination of a fast-acting blood schizonticide and a gametocytocidal drug has been advocated [1, 2].

The role of primaquine as a gametocytocidal drug in *P. falciparum* infections is controversial. Mefloquine has been shown to be effective in the prophylaxis and treatment of infections with multi-drug resistant *P. falciparum* [3, 4] and its use in combination with the gametocytocidal drug primaquine could be of great value in the control of malaria, provided that there was no adverse effect due to a drug interaction. Primaquine does inhibit hepatic microsomal enzymes, both *in vitro* and *in vivo* [5, 6], and since mefloquine is metabolized in the liver to a carboxylic acid [7, 8], perhaps via isozyme(s) of cytochrome P450 (Na Bangchang, unpublished observations), it was important to ascertain if the co-administration of primaquine would alter the pharmacokinetics of mefloquine. The present study was conducted to examine this pharmacokinetic possibility.

Subjects and methods

Eight healthy Thai men, aged 25–52 y, weighing 47–64 kg, with no history of hepatic or renal disease were recruited. None was taking regular medication and none took any other drug during the study. Written informed consent was obtained and the study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University.

The study was of cross-over design, and each subject attended on two occasions, at least 12 weeks apart, and remained in hospital for the first 5 days of the study. On the first occasion, they were randomized to receive either mefloquine 750 mg or mefloquine 750 mg and primaquine 45 mg. All the drugs were given as single oral doses. The subjects fasted overnight and until 2 h after dosing. Blood samples (4 ml collected into lithium heparin plastic tubes) for the determination of whole blood mefloquine concentrations were obtained initially through an indwelling intravenous catheter in a forearm vein, and subsequently by individual venepunctures. Samples were collected at 0, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 18, and 24 h, and on Days 2, 3, 4, 7, 14, 21, 28, 35, 42, and 56, and were stored at −70 °C until analysis.

Adverse effects (including gastrointestinal, central nervous system and cardiovascular effects) were monitored by Questionnaire, daily for 7 days and then weekly until day 56. A neurological examination was performed and depression was assessed by the Hamilton rating scale [9].

Baseline investigations included full blood and serum biochemistry examinations, a 12-lead ECG, and blood pressure. The same tests done 1, 2, 4, 6, 8 and 24 h after dosing, daily for 7 days, and then weekly until Day 56.

The whole blood mefloquine concentration was analysed by HPLC [10]; the lower limit of detection of 50 $ng \cdot ml^{-1}$, and the inter-assay coefficients of variation were 4.2 % at 100 $ng \cdot ml^{-1}$ and 5.7 % at 600 $ng \cdot ml^{-1}$.

Using non-linear regression analysis (PC-NONLIN), a two compartment model with first-order absorption was fitted to the blood drug concentration versus time data. The apparent total clearance (CL/f), and the apparent volume of distribution (V_z/f) were calculated using standard methods. The AUC was calculated by the linear trapezoidal method with extrapolation to infinity. Statistical analysis was by Wilcoxon's signed rank test.

Table 1. Pharmacokinetics of mefloquine (mean with SD) in eight volunteers after mefloquine alone or mefloquine plus primaquine

	Mefloquine	Mefloquine + primaquine	95 % CI
C_{max} ($ng \cdot ml^{-1}$)	1161 (120)	1179 (153)	−222, 126
t_{max} (h)	5.6 (2.8)	6.4 (3.6)	−6.0, 2.0
AUC ($\mu g \cdot ml^{-1} \cdot day$)	20.0 (3.8)	20.2 (4.8)	−4.5, 4.7
$t_{1/2\alpha}$ (h)	3.1 (0.8)	3.2 (1.1)	−1.2, 0.7
$t_{1/2}$ (h)	19.7 (3.2)	17.0 (2.6)	−1.5, 4.5
CL/f ($ml \cdot min^{-1} \cdot kg^{-1}$)	0.48 (0.07)	0.51 (0.11)	−0.13, 0.11
V_z/f ($l \cdot kg^{-1}$)	19.6 (4.0)	19.2 (4.7)	−5.1, 5.7

Results

All the volunteers had normal physical examinations and baseline laboratory investigations.

Adverse effects

The most striking adverse effect was diarrhoea, which five subjects experienced after mefloquine alone and/or mefloquine plus primaquine. It was self-limiting and required no treatment. There were no differences on the Hamilton rating scale between mefloquine alone and mefloquine plus primaquine. Sinus arrhythmia was found in the ECG from one volunteer on Day 21 after mefloquine alone.

Pharmacokinetics

The pharmacokinetics of mefloquine (Table 1) did not differ between the two groups. The results and the 95% confidence intervals of the differences in the means are shown in Table 1.

Discussion

The co-administration of primaquine with mefloquine produced adverse effects similar to those of mefloquine alone. CNS dysfunction is an important adverse effect of mefloquine [3, 11–12], but no behavioural change was found in any of the volunteers, and there was no increased incidence of neurological symptoms when primaquine was added. Dizziness was reported by three subjects taking mefloquine alone but not after the drug combination. Nausea was reported by two and one subjects, respectively, given mefloquine alone and mefloquine plus primaquine. The number of subjects in the study was small, so it is not possible to draw wide-ranging conclusions about the adverse effects of mefloquine. However, there was no evidence of worsening of the adverse effects when primaquine was added.

Primaquine did not alter the pharmacokinetics of mefloquine in Thai volunteers. The data for mefloquine alone are comparable to those previously published [13]. Thus, despite the evidence that primaquine can inhibit drug metabolism [5–6], it did not alter the pharmacokinetics of mefloquine *in vivo*. Further information is needed about the enzyme(s) involved in the formation of the carboxylic acid metabolite, but the present results do suggest that, at least at the concentrations of primaquine present in the liver after a single 45 mg dose, that enzyme(s) is not inhibited to significant extent. It should also be noted that primaquine has a very short half-life compared to mefloquine [14].

The results suggest that there is no pharmacokinetic reason why in areas where there is heavy transmission of falciparum malaria, the combination of mefloquine and primaquine should not be given to a patient who has a positive blood smear with the asexual form and gametocyte of *P. falciparum*.

Acknowledgements. The study was supported by the UNDP/World BANK/WHO Special Programme on Research and Training. JK is in receipt of Mahidol University-Wellcome Trust Research Fellowship. KN is in receipt of a UNDP/World Bank/WHO Special Programme on Research and Training Fellowship.

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