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Plasma and whole blood mefloquine concentrations during treatment of chloroquine-resistant falciparum malaria with the combination mefloquine–sulphadoxine–pyrimethamine

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Mefloquine–sulphadoxine–pyrimethamine (MSP) in combination has proved effective against multiple-drug-resistant falciparum malaria, but nothing is known about mefloquine absorption when it is given in this formulation. Nine Thai patients, aged 15–51 years with uncomplicated chloroquine-resistant falciparum malaria, took 11.2–16.7 mg of mefloquine base per kilogram bodyweight as MSP tablets. All patients responded to treatment with fever and parasite clearance times of 61 ± 29 h (mean ± s.d.) and 52 ± 24 h, respectively. The mean apparent absorption half-time ($t_{½}$abs) of mefloquine was 4.89 h (range 2.25–9.72) and mean peak plasma concentration was 1815 ng ml^{-1} (range 725–3368). Peak plasma mefloquine concentrations in three patients who vomited within 2 h of treatment were 725, 956 and 1972 ng ml^{-1}. There was no significant difference between plasma and whole blood mefloquine concentrations during the first 48 h of treatment. Based on the elimination of parasitaemia, the plasma mefloquine concentrations are adequate for therapy of uncomplicated falciparum malaria although the relationship between plasma concentrations and therapeutic efficacy of mefloquine requires further study.

Keywords mefloquine sulphadoxine pyrimethamine absorption

Introduction

Multiple drug-resistant falciparum malaria is a major problem in South East Asia. In Thailand approximately 90% of cases are resistant to chloroquine (Harinasuta *et al.*, 1982). Although mefloquine combined with sulphadoxine–pyrimethamine was shown to be effective against drug resistant malaria (Harinasuta *et al.*, 1983; Meek *et al.*, 1986) little information is available about mefloquine pharmacokinetics during the treatment of acute infections.

Early volunteer studies showed that the bioavailability of mefloquine was improved when the drug was given as a suspension rather than as tablets (Desjardins *et al.*, 1979). However, modified tablet formulations resulted in better absorption in volunteers (Schwartz *et al.*, 1982).

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Data in patients are limited but a comparison of mefloquine pharmacokinetics in healthy Caucasian and Thai malaria patients has revealed important differences (Looaresuwan, unpublished observations). For example, peak mefloquine concentrations were higher and elimination half-lives were shorter in subjects with malaria. The relative importance of the two variables (ethnic difference and disease) has not been reported. Also, to date, the pharmacokinetics of the formulation of mefloquine proposed for world wide distribution (mefloquine– sulphadoxine–pyrimethamine MSP) have not been examined.

Drug malabsorption may be a cause of treatment failure in malaria although this may be wrongly attributed to drug resistant parasites (Herzog *et al.*, 1982). When the treatment of a potentially lethal infection depends on single dose oral therapy, it is mandatory that absorption of the drug is reliable and that therapeutic plasma concentrations are achieved.

To investigate mefloquine absorption when the drug is administered as MSP tablets, we measured plasma mefloquine concentrations in Thai patients with acute, uncomplicated falciparum malaria.

Methods

Patients aged more than 15 years with uncomplicated *P. falciparum* malaria were admitted to the ward at Kanchanaburi Provincial Hospital, Thailand. Written informed consent was obtained from all patients. The study was approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok. Height, weight, full clinical history and examination were recorded on standard forms. Baseline investigations included parasite counts, full blood examination, serum biochemistry and screening for plasma quinine and mefloquine.

Exclusions

Patients were excluded from the study if they had a history of recent antimalarial treatment; were pregnant; had a history of gastrointestinal disease, liver disease or previous surgery to the upper gastrointestinal tract; had detectable antimalarial drug in blood or urine; had an asexual parasitaemia greater than 5%, impaired consciousness, jaundice, oliguria or severe vomiting.

Treatment

Mefloquine–sulphadoxine–pyrimethamine (250 mg–base–500 mg–25 mg) combination tablets were given according to weight in a single oral dose with a glass of water as follows (WHO, 1984). 20–30 kg 1½ tablets, 31–45 kg 2 tablets, ⩾ 45 kg 3 tablets.

Study programme

Blood was taken through an indwelling intravenous teflon catheter kept patent with heparinized saline. Blood was taken before and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 48 h, then daily after taking mefloquine until discharge from hospital (range 4–10 days). Samples were collected into glass tubes containing oxalate and the plasma which was separated within 30 min was then stored in plastic tubes at −70° C until analysis.

Parasite counts were performed every 8 h for 48 h then twice daily until the parasitaemia had cleared.

Analysis

Mefloquine in plasma was assayed by high performance liquid chromatography (h.p.l.c.; Riviere *et al.*, 1985). For the assay of mefloquine in whole blood the extraction procedure was modified as follows; To samples of blood (1 ml) containing WR 184,806 as internal standard ([±-2,8-bis-trifluoromethyl)-4-[1-hydroxy-3-(*N*-tertbutylamino)-propyl]quinoline] phosphate; 400 ng) was added acetonitrile (2 ml) followed by vortex mixing for 30 s and centrifugation at 1000 *g* for 5 min. The acetonitrile phase was transferred to clean tubes and glycine buffer (0.1 M; pH 9.2; 2 ml) was added. After vortex mixing for 15 s the mixture was extracted with dichloromethane (6 ml) and the extracts assayed by h.p.l.c. (Riviere *et al.*, 1985).

Standard curves were prepared by adding known quantities of mefloquine (50–1000 ng) to either plasma or whole blood containing internal standard (400 ng). The limit of detection of mefloquine in both plasma and blood was 20 ng ml^{-1}. The interassay coefficient of variation of blood samples containing known quantities of drug was 4.1% at 100 ng ml^{-1} and 5.7% at 600 ng ml^{-1}.

Pharmacokinetic analysis

For determination of the apparent absorption half-life ($t_{½}$abs), plasma concentration-time data were analysed by an iterative nonlinear curve fitting programme (NONLIN) with a non-weighted least squares criterion of fit. The peak plasma concentration (C_{max}) and time to peak

(t_{max}) were interpolated from the individual plasma drug concentration-time profiles.

Data are presented as mean ± s.d.

Initial estimates of the apparent absorption and elimination rate constants (*ka* and *k*) obtained by the method of residuals were used for the fitting process.

Results

Nine patients, six of whom were male, were studied (Table 1). All gave a history of fever lasting 1–5 days and all but one patient were febrile (mean 38.6° C, range 36.7–41.1). Admission laboratory values were: asexual parasitaemia, geometric mean 12,145 μl^{-1} (range 468–98, 258), haematocrit 37.1 ± 1.4% (mean ± s.d.), white cell count, 4922 ± 1591 μl^{-1}, blood urea nitrogen 18.2 ± 6.1 mg dl^{-1} serum creatinine 1.0 ± 0.2 mg dl^{-1} and total bilirubin 1.1 ± 0.5 mg dl^{-1}.

Therapeutic response

All patients responded to treatment with fever and parasite clearance times of 61 ± 29 h and 52 ± 24 h respectively. Three patients (1, 7 and 8) vomited after taking MSP but no other adverse effects were seen.

Plasma and whole blood mefloquine concentrations

Concentration profiles are shown in Figure 1. The mean plasma mefloquine concentration exceeded 500 ng ml^{-1} 3 h after taking the tablets. The peak plasma mefloquine concentration in patient one, who vomited 80 and 205 min after three tablets was 725 ng ml^{-1}; in patient 7, who vomited 39 and 220 min after three tablets, 956 ng ml^{-1}; while in patient 8, who vomited 70 min after two tablets, it was 1972 ng ml^{-1}. The mean peak plasma mefloquine concentration in the six patients who did not vomit was 2114 ± 777 ng ml^{-1}. Individual pharmacokinetic values are shown in Table 1. Mefloquine concentrations in plasma tended to exceed those in whole blood during the first 48 h of therapy but this difference was never statistically significant.

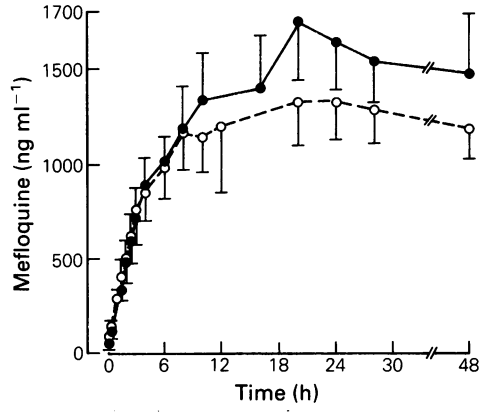

Figure 1 Plasma (•) and whole blood (○) concentrations (mean ± s.e. mean) of mefloquine in patients receiving mefloquine in combination with sulphadoxine and pyrimethamine.

Discussion

An examination of the three pharmacokinetic parameters apparent $t_{½}$ abs, t_{max} and C_{max} reveals some interesting and important features of the plasma concentration-time profile of mefloquine

Table 1 Patient details and pharmacokinetic parameters

Patient	Age (years)	Sex	Weight (kg)	Dose (mg)	Dose (mg kg^{-1})	Apparent $t_{½}$abs (h)	Plasma C_{max} (ng ml^{-1})	Plasma t_{max} (h)	Whole blood C_{max} (ng ml^{-1})	Whole blood t_{max} (h)
1	32	M	57	750	13.2	5.05	725	20	611	20
1	35	M	49	750	15.3	3.52	1405	20	949	20
3	30	M	37	500	13.5	3.12	1241	20	1286	12
4	15	F	45	750	16.7	9.72	1987	24	1343	8
5	32	M	49	750	15.3	4.27	2514	20	2352	20
6	19	M	67	750	11.2	6.13	2168	24	1586	24
7	22	M	57	750	13.2	3.05	956	24	948	24
8	51	F	38	500	13.2	2.25	1972	30	1470	30
9	18	F	—	750	—	6.86	3368	22	2425	24
Mean	28.2					4.89	1815	22.7	1442	19.1
s.d.	11.2					2.35	829	3.3	613	8.7

seen following oral administration of MSP to nine patients with uncomplicated chloroquine resistant falciparum malaria. The apparent absorption half-life of mefloquine ranged between 2.25 and 9.72 h and mean plasma concentrations exceeded 500 ng ml^{-1} 3 h after taking the tablets. Peak plasma drug concentrations between 725 and 3368 ng ml^{-1} were obtained and there was a good clinical and parasiticidal response in all patients (fever and parasite clearance times of 61 ± 29 and 54 ± 24 h respectively). With reference to Figure 1 it is clear that the initial rapid increase in plasma drug concentration (0–5 h) is followed by a slower increase to peak (mean time to peak 22.7 h). It should be noted that $t_{½}$ abs is a hybrid parameter involving both absorption from the gut into the portal circulation and transit through the liver (hence 'apparent' $t_{½}$ abs) and it seems probable that for mefloquine with a long elimination half-life (15–33 days; Schwartz *et al.*, 1982) transit through the liver is a slow process.

The apparent absorption half-lives in these malaria patients were similar to those reported in Caucasian volunteers (Desjardins *et al.*, 1979) but the peak drug concentrations were higher. Looareesuwan (unpublished observations) and Chongsuphajaisiddhi (personal communication) also found significantly higher mefloquine concentrations in Thai malaria patients compared with healthy Swiss volunteers.

Although the plasma mefloquine concentrations found in this study cleared the parasitaemia in all cases, the minimum mefloquine concentration required to cure chloroquine resistant falciparum malaria in Thailand remains uncertain. Recrudescence of falciparum malaria has been documented in patients with plasma mefloquine concentrations between 228 and 776 ng ml^{-1} 7 days after starting treatment (Harinasuta *et al.*, 1985). Estimates of minimum therapeutic concentration based on *in vitro* testing could be particularly unreliable for mefloquine because of its tendency to bind to cell membranes, proteins and plastic. *In vitro* minimum inhibitory concentrations using the macro technique were reported as 41 to 414 ng ml^{-1} in 1981 (Chongsuphajaisiddhi, personal communication) and are likely to be gross underestimates. More information derived from human studies is needed.

Mefloquine has a high affinity for red cell membranes (Fitch *et al.*, 1979). *In vitro*, red cell mefloquine concentrations may be sixty times those in a bathing medium of buffered saline (San George *et al.*, 1984). We have found no difference between whole blood and plasma mefloquine concentrations during the first 48 h of therapy for malaria. Presumably this is explained by extensive plasma protein binding of mefloquine. If this finding is confirmed when mefloquine concentrations are measured at longer intervals after dosing, either whole blood or plasma will be suitable for assaying drug concentrations. Whether this holds true when other drugs, such as quinine (Chanthavanich *et al.*, 1985), are given simultaneously also requires investigation.

We have not studied sufficient numbers of patients to be certain of the effect of vomiting on mefloquine absorption. Two of our patients who vomited 39 and 80 min after taking MSP tablets had appreciably lower plasma mefloquine concentrations than those who did not. Vomiting within a few hours of swallowing MSP or mefloquine alone has been associated with treatment failure (Harinasuta *et al.*, 1985) and even death (Meek, personal communication). Absorption of mefloquine in uncomplicated malaria appears reliable but the lower plasma mefloquine concentrations found in a study of severely ill patients might represent potentially serious malabsorption (Chanthavanich *et al.*, 1985). Until more is known a judicious approach would be to observe all patients given a treatment dose of MSP and to assume that, if vomiting occurs within 1 or 2 h, drug absorption might be affected. Second doses of MSP tablets could produce toxicity but the dangers of inadequate treatment for falciparum malaria probably override this. Because of the toxicity attributable to sulphadoxine (Miller *et al.*, 1986) removal of the sulphadoxine pyrimethamine components may reduce the potential toxicity of MSP treatment.

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