PHARMACOKINETICS OF PROPHYLACTIC MEFLOQUINE

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Abstract. The pharmacokinetics of the prophylactic dose of mefloquine (Lariam® : 500 mg every 4 weeks, with a loading dose of 750 mg on the first week) was studied in six healthy Thai male volunteers. Mefloquine was well tolerated during the study period of 16 weeks. The only side-effects found were nausea and diarrhea in 2 volunteers after the first dose of mefloquine.

The mean minimum concentration of mefloquine at steady state ranged from 290 to 460 ng/ml. The maximum concentration on week 16 after the last dose was 1558 ± 48 ng/ml at the mean time of 38 ± 19 hours. The others pharmacokinetic parameters obtained were : absorption half life = 6.6 ± 3.0 hours; distribution = 5.1 ± 3.1 days; terminal half life = 12.9 ± 2.2 days; apparent volume of distribution = 10.5 ± 2.3 l/kg; area under the concentration-time curve = 26.9 ± 2.2 mg/dl.

Although this prophylaxis regimen is ideal when considering the compliance, the minimum concentration obtained was much too low for optimum therapeutic concentration. We therefore suggest that weekly prophylaxis schedule should be a better regimen as the difference between minimum and maximum mefloquine concentration would be smaller.

INTRODUCTION

Malaria is a deadly disease which constitutes one of the most serious public health problems in Thailand. Approximately 60% of malaria cases are caused by *Plasmodium falciparum,* almost all are chloroquine resistant, over 80% and 30% are sulfadoxine-pyrimethamine and quinine resistant, respectively. The use of mefloquine has been shown to be effective against multi-drug resistant falciparum malaria (Harinasuta *et al,* 1983; Karbwang and White 1990). This drug seems to be the only available drug for prophylaxis in Thailand, it is therefore important to define the pharmacokinetics and blood levels of multiple dosing of mefloquine in the Thai population. It is hoped that the information gained from the present study will assist in the design of appropriate dosage regimens for malarial prophylaxis.

MATERIALS AND METHODS

Subjects

Six healthy Thai male volunteers aged between 24 and 43 years and weight ranging between 51 and 62 kg with no history of liver or kidney diseases were included in the study. No other concurrent drugs were taken during the study period. Written informed consent was obtained from all volunteers.

All subjects underwent physical examination, routine blood examination (complete blood count and biochemistry), plain chest x-ray, electrocardiogram and urinalysis prior to recruitment. All subjects who had normal physical examination and normal findings on laboratory investigation were admitted to the Bangkok Hospital for Tropical Diseases for one night on each of two occasions. The first occasion was on the first day of drug administration and the second occasion was on the 16th week of the study. The patients had weekly follow-up until week 16 then daily during week 16 then weekly again until week 21.

Drug administration

Three tablets of mefloquine (Lariam®-Hoffman La Roche, 250 mg/tablet) were given to each volunteer on day 0. Subsequent doses of two

tablets of Lariam® were given at four weekly with the last dose on week 16.

Blood collection

Four ml of whole blood was sampled weekly for mefloquine concentrations before administration of the next prophylactic dose until week 16. On week 16, a teflon cannula was inserted into the antecubital vein for 24 hours for frequent blood sampling. Blood was sampled at 2, 4, 8, 12, 16, 20, 24, 48, 72, 120, 168 hours and then weekly for another 4 weeks after dosing on week 16.

Laboratory investigations

Complete blood count and biochemistry were performed every four weeks.

Mefloquine analysis

Whole blood mefloquine was analysed by HPLC (Karbwang *et al,* 1989).

Adverse effects

Adverse effects were recorded at the time of blood sampling for mefloquine concentration.

Data analysis

Whole blood mefloquine concentration-time data was analysed by PC-NONLIN, using a multiple dosing two compartment model.

RESULTS

Six healthy volunteers were included in the study. Adverse effects consisted of nausea and diarrhea after the first dose of mefloquine (ie at 750 mg dosing) in 2 volunteers. The symptoms occured within two to three hours after dosing, however, they were transient and required no specific treatment. No adverse effects were found during the subsequent four doses. There were no changes in biochemistry nor blood profiles during 21 weeks of observation. No behavioral changes were noticed in any of the volunteers during the study period.

Mean whole blood mefloquine concentrations on each week are presented in Fig 1. The mean minimum concentrations of mefloquine (concentration at pre-dosing) ranged from 290-460 ng/ml. The maximum concentration (Cmax) obtained on week 16 was 1558 ± 48 ng/ml (mean ± SD) at mean time to maximum concentration (Tmax) of 38 hours.

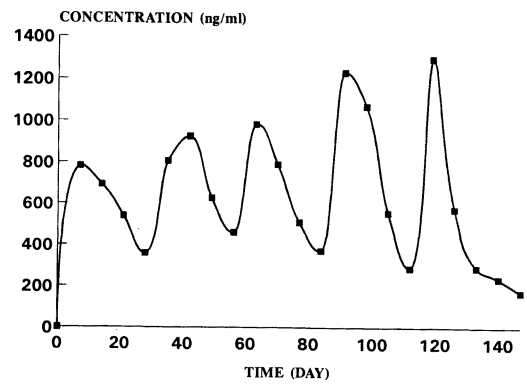

Fig 1—Mean mefloquine concentrations.

Pharmacokinetic parameters of multiple dosing mefloquine are presented in Table 1. Mean absorption half-life was 6.6 hours, the distribution half-life (Td 1/2) and terminal elimination half-life (Tt 1/2) were calculated to be 5.1 and 12.9 days, respectively. The mean apparent volume of distribution was 10.5 l/kg. The area under concentration-time curve- α (AUCo- α) was 26.9 mg/dl.

DISCUSSION

Mefloquine (Lariam®) 500 mg every four weeks (with a loading dose of 750 mg on the first week) as prophylaxis was well tolerated in healthy volunteers. There were no changes in liver, kidney or blood profiles, suggesting that mefloquine is safe as prophylaxis using the present dosage regimen. However, long-term use, ie more than 6 months of mefloquine may require further evaluation as reports on neuropsychiatric reactions from mefloquine are increasingly frequent.

The minimum concentration of mefloquine obtained from this study ranged between 290 and 460 ng/ml. The protective concentration of mefloquine against malaria infection has not been described. However, patients with a concentration of

Table 1

Pharmacokinetics of mefloquine

Subjects	Cmax (ng/ml)	Tmax (hours)	Tab 1/2 (hours)	Td 1/2 (days)	Td 1/2 (days)	Vd (1/kg)
1	1528	24	2.6	4.0	10.0	13.8
2	1641	48	9.6	11.4	11.6	8.5
3	1528	72	8.2	2.7	12.9	9.2
4	1605	48	10.1	6.1	12.9	8.2
5	1534	24	3.4	2.0	17.3	12.3
6	1512	16	5.5	4.2	12.6	11.2
Mean	1558	38	6.6	5.1	12.9	10.5
SD	48	19	3.0	3.1	2.2	2.3

Tab 1/2 = Absorption half-life
Td 1/2 = Distribution half-life
Tt 1/2 = Terminal half-life

greater than 500 ng/ml on the first day after treatment were found to be associated with greater than 95% cure rate (Warrell *et al,* unpublished observations). In a recent study (Karbwang *et al,* 1991), it was shown that healthy volunteers with 250 mg of mefloquine in combination with 500 mg sulfadoxine and 25 mg of pyrimethamine as Fansimef® tablets monthly were free from malaria during a 19 week study period. The minimum concentration from that study was 100-140 ng/ml. However, we cannot consider these concentrations as inhibitory since the study was performed during the low transmission season and the volunteers were exposed to malaria only 2-3 days/week. Pharmacokinetics of mefloquine from the multiple dosing schedule in this study are in agreement with a recent study of prophylactic mefloquine at 125 mg weekly in healthy Thai volunteers (Karbwang, unpublished data). The Tab 1/2 was 6.3 ± 3.6 hours and the Tt 1/2 was 14.2 ± 3.3 days. Mean Cmax was 836 ng/ml and the minimum concentration at steady state was 393 ng/ml. The dose of that study was 125 mg weekly, ie a total dose of 500 mg for four weeks which is equivalent to the dose used in the present study. However, lower mean minimum concentrations and higher mean maximum concentrations were obtained in the present study when compared to those found in the weekly regimen. Although once a month medication is an ideal regimen for prophylaxis, the minimum concentration obtained in this study is much lower than the therapeutic concentrations. Mefloquine is not a causal prophylaxis, it is therefore important that the drug concentrations should be more or less steady at the level that is needed to kill the parasites that first appear in the erythrocytes to prevent further development, thus stopping the sequestration and complications. With increasing numbers of mefloquine resistant strains of *P. falciparum,* a dose of 250 mg weekly has been suggested (Nosten *et al,* 1990), corresponding to 1000 mg monthly (4 tablets of Lariam®). We suggest that weekly prophylaxis should be a better regimen as the differences of minimum and maximum drug concentrations would be smaller and the peak concentrations would not be too high thus minimising the adverse effects. In addition, compliance will be poor with a monthly regimen as 4 tablets of mefloquine would result in a high percentage of nausea and vomiting. A recent prophylactic study in pregnant women at a dose of 250 mg weekly showed 100% protection (Nosten, personal communication), however, the parasites in that study were not as highly resistant to mefloquine as are those in Eastern border of Thailand (where prophylaxis is needed). It is therefore necessary to do further studies to define the protective concentrations against malaria infection. Such studies should be carried out in a high transmission area where the infection rate is close to 100% with the existence of highly mefloquine resistant strains of *P. falciparum.*

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