PHARMACOKINETICS OF MEFLOQUINE IN TREATMENT FAILURE

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Abstract. The pharmacokinetics of mefloquine at the therapeutic dose of 750 mg single orally were compared between cured and recrudescent patients with acute uncomplicated falciparum malaria. Mefloquine was well-tolerated during the study. The side-effects found were nausea, vomiting and diarrhea. Five patients showed R-I and two showed R-II types of response. All recrudescent patients came from the eastern border of Thailand. The time taken to clear the parasites (PCT) was significantly longer in patients with recrudescence (99.6 ± 36.9 and 63.0 ± 8.9 hours); however, there was no difference regarding fever clearance time (FCT : 39.0 ± 16.1 and 31.0 ± 21.3 hours).

The maximum concentration (Cmax) and the concentration on the first and second days in cured patients were significantly higher than those of treatment failure patients. Other pharmacokinetic parameters appeared to be similar in both groups.

The present study indicates the existence of mefloquine-resistant falciparum malaria in the eastern border of Thailand. Inadequate mefloquine concentration may play an important role in this aspect. In addition, this study also suggests that Cmax or the concentrations on the first or second day of treatment may be used as guidelines to predict the outcome of treatment.

INTRODUCTION

During the past years, there have been several failure of mefloquine treatment (Boudreau *et al,* 1987), it is not clear whether this represents genuine resistance or problems with vomiting, resulting in inadequate absorption. It has been shown recently that the patients who vomited within one hour after treatment had significantly lower mefloquine concentrations (Karbwang *et al,* 1991a). Furthermore, the therapeutic concentrations of mefloquine in areas with multi-drug resistance are not known. We have carried out a pharmacokinetic study of mefloquine in uncomplicated falciparum malaria patients with curative response and treatment failure to resolve this issue.

MATERIALS AND METHODS

Patients

Eighteen Thai adult male patients with acute uncomplicated falciparum malaria (asexual form parasitemia of less than 5%), aged between 17 and 55 years, weight ranged 46-59 kg with no history of liver or kidney diseases were recruited into the study. No other concurrent drugs were taken during the study. Written informed consent to participation in the study was obtained from all patients. The study was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Each patient underwent physical examination, routine blood examination and blood chemistry investigations, plain chest x-ray, urinalysis and electrocardiogram (ECG). Plasma was taken for baseline antimalarials ie quinine and mefloquine. All patients were admitted into the Bangkok Hospital for Tropical Diseases for 42 days.

Treatment

Mefloquine 750 mg was given to the patients as an oral single dose. The drug was administered with a glass of water under supervision. Patients

who had R-I, R-II types of response treated with standard regimen of quinine 600 mg (salt) three times/day plus tetracycline 250 mg four times/day for 7 days.

Hematological and biochemical investigations

Blood examination and biochemistry were done on day 0, day 2, day 4, day 7 then weekly until day 42.

Parasite count

Parasite count was performed twice daily until negative, then once daily until day 42.

Adverse effects

All adverse reactions during the study were recorded with the date and time when they occurred and disappeared. The severity was graded into 1, 2 and 3. These changes included gastrointestinal, central nervous, cardiovascular, dermatological, hematological systems and other changes possibly attributable to mefloquine. Frequency of vomiting and diarrhea was recorded on day 0, day 1, day 2, day 3 and day 4. History of itching/skin rash after any drugs and itching/skin rash after mefloquine, intensity and duration of rash were recorded.

Blood pressure (BP) measurement was performed at 4 hour-interval during the first week then daily until day 42.

Blood collection for pharmacokinetic study

Three ml of whole blood was taken for mefloquine at 1, 2, 4, 6, 8, 12, 18 and 24 hours then daily until day 7, followed by weekly until day 42.

Mefloquine analysis

Whole blood mefloquine level was analysed by high performance liquid chromatography (Karbwang *et al* 1989).

Pharmacokinetic analysis

Whole blood mefloquine concentration-time data were analyzed by an iterative non-linear curve fitting program (PC-NONLIN) with a non-weighted least square criterion of fit.

Data analysis

The patients were included for efficacy assessment when the patients have completed the 42-day study period. The parameters that used in determination of efficacy included parasite clearance time (PCT), fever clearance time (FCT) and the occurence of side-effects.

Whole blood concentrations, maximum concentration (Cmax) and pharmacokinetic parameters were compared between patients with cure and recrudescence.

Statistical analysis was performed by Mann-Whitney U test.

RESULTS

Eighteen patients were included into the study. Twelve patients contracted infection from the eastern border of Thailand (high degree of mefloquine resistance) and six from the western border. Seven patients had recrudescence and all came from the East. R-II type of response was seen in two of them. These two patients were non-immune immigrants from the Northeast of Thailand and had been in the endemic area for less than two months.

Parasite count and baseline laboratory on admission are comparable in patients with cure and recrudescence (Table 1).

The PCT in patients with cure and recrudescence were 63.0 ± 8.9 and 99.6 ± 36.9 hours, respectively. The time taken to clear the parasite was significantly longer in patients with recrudescence. However, there was no difference regarding FCT (Table 1).

Six patients experienced adverse effects which included nausea, vomiting and diarrhea. There is no correlation between the outcome of the treatment and vomiting or diarrhea.

Whole blood concentration profiles of mefloquine in patients with cure and treatment failure are shown in Fig 1. The Cmax, the concentrations on the first and second days in cured patients were significantly higher than those of treatment failure patients. However, the concentrations on the third day onward were not different. Pharmacokinetic analysis (Table 2) showed no differences

Table 1

Clinical date.

Parameters	Cure	Recrudescence
Age (year)	24.2 ± 10.9	25.7 ± 4.6
Weight (kg)	52.1 ± 4.4	54.6 ± 3.2
Admission parasites (/cumm)	8,900 – 12,450	4,567–15,400
WBC (/cumm)	6,545 ± 2,687	5,507 ± 1,935
Hct (%)	31.6 ± 2.9	31.2 ± 5.9
PCT (hours)	63.0 ± 8.9	99.6 ± 36.9
FCT (hours)	31.0 ± 21.3	39.0 ± 16.1

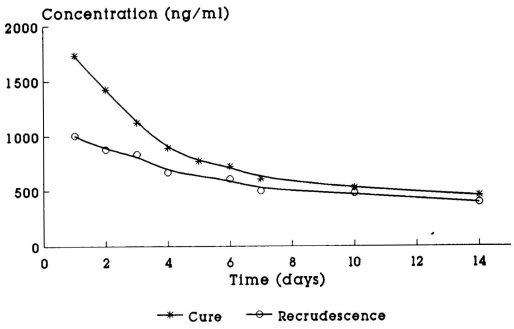

Fig 1—Mephloquine concentration in patients with cure and recrudescence.

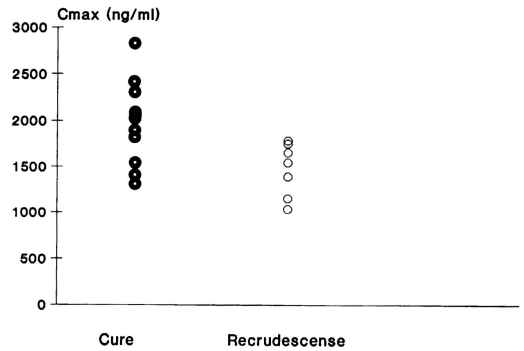

Fig 2—Cmax in patients with cure and recrudescence.

Table 2

Pharmacokinetic parameters of mefloquine in patients receiving mefloquine 750 mg as a single oral dose.

Pharmacokinetic parameters	Cure	Recrudescence
Cmax (ng/ml)*	1,923 ± 373	1,391 ± 466
Tmax (hours)	15.8 ± 6.9	15.2 ± 8.9
T1/2a (hours)	6.1 ± 4.2	4.8 ± 2.5
AUC (μg.day/ml)	22.08 ± 14.15	19.91 ± 9.54
T1/2 (days)	12.7 ± 5.5	10.9 ± 5.2
Cl/f (ml/min/kg)	0.574 ± 0.226	0.534 ± 0.262
Vd/f (l/kg)	9.78 ± 4.47	7.44 ± 2.18

* Significant difference between cure and recrudescence with p-value < 0.05

in time to maximum concentration (Tmax), absorption half-life (T1/2a), area under concentration-time curve (AUC), terminal half-life (T1/2), clearance (Cl/f) and volume of distribution (Vd/f).

DISCUSSION

It is clearly seen from this study the importance of Cmax and the concentrations on the first two days after treatment. It may be possible to predict the outcome of the treatment by monitoring the Cmax or the concentrations on the first 2 days of treatment. The Cmax of over 1800 ng/ml is less likely to reflect recrudesced cases (Fig 2). However, host and parasite factors may play major roles in the treatment of malaria infection. Firstly, certain strains of malaria parasite are resistant to mefloquine in which higher mefloquine concentration is required, ie those patients who contracted malaria from the eastern border. Secondly, the patients may have some immunity against malaria after long exposure to infection; these patients may not require high mefloquine concentrations when compared to those with no immunity against malaria.

The findings of the present study are consistent with those reported by Boudreau *et al,* (1990) where they found the Cmax to be higher in cured patients when compared to recrudescent patients. These suggest that documentation of mefloquine resistant strains of falciparum malaria requires

comfirmation of adequacy of mefloquine absorption by the host. The patients with recrudescence in this study may have had incomplete absorption with a subsequently relatively low Cmax and concentrations on the first and second days when compared to those of sensitive responses.

The discrepancy of mefloquine concentrations among patients who have been treated with mefloquine may have had occurred in many of the previous studies but there were no differences in the response. This may be due to the fact that falciparum parasites in those studies were still sensitive to mefloquine during that period. The requirement of mefloquine concentration for killing the parasites was lower and adequate concentration could be obtained, even with incomplete absorption. This conclusion is supported by the findings of *in vitro* sensitivity that falciparum parasites along the eastern border are highly resistant to mefloquine (Rooney, personal communication; Thaithong, unpublished observation). The MIC (minimum inhibitory concentration) of mefloquine with the isolates obtained from the eastern border was shown to increase rapidly during this year (Thaithong, unpublished observation).

The slower PCT in patients with recrudescence supports the existence of mefloquine resistant falciparum malaria. However, inadequate absorption of mefloquine is also responsible for treatment failure in this study. The requirement of mefloquine concentration was sufficient with relatively complete absorption as seen in those patients with sensitive responses.

Other pharmacokinetic parameters of mefloquine in the present study are similar to previous studies (Karbwang *et al,* 1988; 1991a) with shorter T1/2 when compared to those obtained from healthy volunteers (Karbwang *et al,* 1988; 1991b).

Recently, it has been shown that vomiting within the first hour resulted in very low mefloquine concentrations (Karbwang *et al,* 1991a) and subsequent treatment failure. However, in this study vomiting showed no influence on mefloquine concentration as all patients vomited a few hours after drug administration.

In conclusion, this study suggests that mefloquine resistant strains of falciparum exist in the eastern border of Thailand and these require higher concentrations of mefloquine than previously needed. As a consequence, incomplete absorption of mefloquine by the host can result in treatment failure. It is also suggested that the best time to monitor mefloquine concentration is during the first two days after treatment.

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REFERENCES

Boudreau EF, Webster HK, Pavanand K, Thosingha L. Type II mefloquine resistance in Thailand. *Lancet* 1982; 2 : 1335.

Boudreau EF, Fleckenstein L, Pang W, *et al.* Mefloquine kinetics in cured and recrudescent patients with acute falciparum malaria and in health volunteers. *Clin Pharmacol Ther* 1990; 48 : 399-409.

Bunnag D, Harinasuta T. The current status of drug resistance in malaria. *Int J Parasitol* 1987; 17 : 169-80.

Karbwang J, Back DJ, Bunnag D, Breckenridge AM. A comparison of the pharmacokinetics of mefloquine in Thai healthy volunteers and in patients with falciparum malaria. *Eur J Clin Pharmacol* 1988; 35 : 677-80.

Karbwang J, Na Bangchang K, Molunto P, Bunnag D. Determination of mefloquine in biological fluids using high performance liquid chromatography. *Southeast Asian J Trop Med Public Health* 1989; 20 : 61-5,

Karbwang J, Na Bangchang K, Bunnag D, Harinasuta KT. Pharmacokinetics and pharmacodynamics of mefloquine in patients with uncomplicated malaria. *Bull WHO* 1991a; 69 : 207-12.

Karbwang J, Na Bangchang K, Back DJ, Bunnag D, Harinasuta KT. Effect of ampicillin on mefloquine pharmacokinetics in Thai subjects. *Eur J Clin Pharmacol* 1991b; 40 : 631-3.