CLINICAL TRIALS OF MEFLOQUINE WITH TETRACYCLINE

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Abstract. A comparative trial of the combination of mefloquine or MSP with tetracycline was carried out in fifty-one adult Thai male patients with acute falciparum malaria. The patients were randomized to receive either the combination of tetracycline (250 mg qid for 7 days) with mefloquine 4 tablets (1,000 mg) or with MSP 4 tablets (one tablet contains 250 mg mefloquine, 500 mg sulfadoxine and 25 mg pyrimethamine).

Fifty patients had a complete 28-day follow-up period. Both regimens produced similar efficacy with no difference in adverse effects. In the mefloquine plus tetracycline group, the cure rate was 72% (18/25). One patient had an RIII response, the others showed initial response to the treatment with FCT and PCT of 40.7 ± 27.4 and 76.2 ± 34.2 hours (mean ± SD) respectively. However, 6 patients developed recrudescence between days 17 and 29 (RI), 3 of these had vomiting.

In the MSP plus tetracycline group, the cure rate was 76% (19/25). The means (± SD) of FCT and PCT were 44.7 ± 38.0 and 80.6 ± 25.0 hours, respectively. Six patients had recrudescence between days 17 and 31 (RI), 2 of these had vomiting.

Although the addition of tetracycline improved the cure rate of mefloquine when compared with standard dose of mefloquine alone (3 tablets), these combinations seem to be useful in areas where alternaative drugs are not available.

INTRODUCTION

The multiple drug resistant strains of falciparum malaria in Thailand are now increasing and spreading (Bunnag *et al,* 1991). New drugs are not yet available to combat this situation. The use of combinations of available antimalarials should be encouraged. It has been demonstrated that the combination of quinine and tetracycline has increased the cure rate from 75% to 95-100% (Bunnag and Harinasuta, 1986). However, the compliance of the patients is a limiting factor in its use. Cinchonism would be expected to be more frequent with the combination as quinine concentrations are increased in the presence of tetracycline (Karbwang *et al,* 1991a). A recent pharmacokinetic study of the combination of mefloquine and tetrycycline showed an increase in maximum concentration (Cmax) and in whole blood concentrations in the first few days after drug administration without any increase in toxicity (Karbwang *et al,* 1992). The use of mefloquine as a single dose in combination with tetracycline for 7 days has become very attractive, particularly with the evidence from a very recent study showing that the patients who were responsive to the treatment had a significantly higher mefloquine concentration on the first two days of treatment than those with recrudescence (Karbwang *et al,* 1991c).

In the light of these data, it is therefore important to assess the efficacy of mefloquine in combination with tetracycline in chloroquine resistant falciparum malaria patients. We have carried out a study to investigate safety and efficacy of this combination. In addition, as mefloquine-sulfadoxine-pyrimethamine (MSP) is widely used in Thailand, we have studied the efficacy of MSP plus tetracycline as well.

MATERIALS AND METHODS

The study was a randomized prospective comparative trial of the combination of tetracycline with mefloquine or MSP.

Patients

Fifty-one Thai adult male patients with acute uncomplicated falciparum malaria (asexual from parasitemia of less than 5%), aged between 17 and 52 years, weight range 45-70 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 participate in the study was obtained from all patients. The study was approved by the Ethics Commuttee 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 or whole blood was taken for baseline antimalarials, *ie* quinine, mefloquine and halofantrine. All patients were admitted into the Bangkok Hospital for Tropical Diseases for 35 days.

Treatment

The patients were randomized and paired according to geographical areas (*ie* eastern, western and others) to receive oral dosage of either mefloquine 4 tablets (250 mg/tablet) as a single dose plus tetracycline 250 mg four times/day for 7 days or MSP 4 tablets as a single dose (one tablet contains 250 mg of mefloquine, 500 mg of sulfadoxine and 25 mg of pyrimethamine) plus tetracycline 250 mg four times/day for 7 days. The first dose of tetracycline was given concurrently with mefloquine of MSP. The drug was administered with a glass of water under supervision.

Patients who had RI or RII responses were treated with a standard regimen of quinine 600 mg (salt) three times/day plus tetracycline 250 mg four times/day for 7 days.

Parasite count

Parasite count was performed twice daily until negative, then once daily until day 28.

Hematological and biochemical investigations

Blood examination and biochemistry were done on days 0, 2, 4, 7 then weekly until day 35.

***In vitro* sensitivity test**

In vitro sensitivity test for chloroquine, quinine, quinidine and mefloquine was performed prior to drug administration.

Blood samples for mefloquine concentration

Whole blood samples were collected for mefloquine concentrations at days 0, 4 and 7.

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 attributed to mefloquine or MSP and/or tetracycline. Frequency of vomiting and diarrhea was recorded on days 0, 1, 2, 3 and 4. History of itching/skin rash (intensity and duration) after any drug were recorded.

Blood pressure (BP) was performed at 4 hour - intervals during the first week then daily until day 35.

Data analysis

Minimum inhibitory concentrations of mefloquine (*in vitro* sensitivity test) were compared with the previous studies.

The patients were included for efficacy assessment when they had completed the 35-day study period. The efficacy and adverse effects were compared between the two therapeutic regimens. The parameters used in the determination included parasite clearance time (PCT), fever clearance time (FCT), cure rate and the occurrence of adverse effects.

Mefloquine concentrations were compared between patients from the easterm and other areas (including western area); mefloquine concentrations in patients with and without vomiting were also compared.

Statistical analysis

Statistical analysis was by Mann-Whitney U test for unpaired samples.

RESULTS

Fifty-one patients with acute uncomplicated falciparum malaria were recruited into the study. Seventy-three percent of the patients came from the eastern border (Thai-Cambodian) of Thailand, where highly multi-drug resistant strains of falciparum malaria exist. The age, weight, the region where they had contracted malaria and baseline laboratory investigations on admission were found to be comparable in both groups. Fifty patients had a complete 35-day follow-up.

Clinical response

Mefloquine plus tetracycline group: Twenty-four patients showed initial response to treatment with FCT and PCT of 40.7 ± 27.4 and 76.2 ± 34.2 hours (mean ± SD), respectively. One patient had an RIII response, this particular patient came from the eastern border and had excessive vomiting on day 0. Six patients had recrudescence between days 17 and 29 (RI), three of these had vomiting. The cure rate was 72%. No patient showed *P. vivax* in their peripheral blood during the follow-up period.

MSP plus tetracycline group: Twenty-six patients were recruited, one patient did not complete the follow-up. All patients showed a good initial response to treatment with FCT and PCT of 44.7 ± 38.0 and 80.6 ± 25.0 hours, respectively. Six patients had recrudescence between days 17 and 31 (RI), two of these had vomiting. The cure rate was 76%. *P.vivax* infection was not found in any of the patients during follow-up.

There was no statistically significant difference between the two study regimens regarding PCT, FCT and the cure rate. No patient from western areas in either group had recrudescence during 35-day follow-up period.

Adverse effects

The adverse effects consisted of nausea, vomiting, diarrhea, dizziness, palpitation and sleeping difficulty (Table 1) which were found to be similar in both groups. None of the subjects showed any sign of neuropsychiatric reaction. No significant changes of complete blood exam or blood biochemistry investigation were found throughout the study period. Bradycardia was a common finding in both groups, it occurred from day 3 onwards and the lowest heart rate was found on day 6. Bradycardia was found more often in mefloquine group (64%) the MSP group (46%). Thirteen patients from each group developed sinus arrhythmia. Three patients had first degree AV-block (Table 2). No other abnormalities on ECG were seen.

In vitro sensitivity test

Forty-four isolates were successfully cultured and tested for minimum inhibitory concentration (MIC) of chloroquine, quinine, quinidine and me-

Table 1

Adverse effects recorded in patients receiving 4 tablets of mefloquine or MSP plus tetracycline (250 mg qid × 7 days).

Adverse effects	Mefloquine + Tetracycline	MSP + Tetracycline
Vomiting	8	9
Abdominal pain	4	0
Diarrhea	4	2
Dizziness	6	5
Flatulance	3	1
Palpitation	5	6
Insomnia	7	5
Tinnitus	1	1
Tremors	2	1

Table 2

ECG findings in patients with mefloquine or MSP plus tetracycline.

ECG findings	Mefloquine + Tetracycline (N = 25)	MSP + Tetracycline (N = 26)
Sinus bradycardia	16	12
Sinus arrhythmia	13	13
First degree AV-block	1	2

Table 3

MIC of chloroquine, quinine, quinidine and mefloquine in patients with falciparum malaria in this study.

Areas	Chloroquine	Quinine	Quinidine	Mefloquine
West	1.3×10^{-6} M	5.5×10^{-6} M	2.0×10^{-6} M	3.4×10^{-7} M
East	1.3×10^{-6} M	4.5×10^{-6} M	1.6×10^{-6} M	4.0×10^{-7} M

floquine (Table 3). Based on WHO criteria for *in vitro* sensitivity, it was evident that all the isolates were resistant to chloroquine. The mean MIC for quinine, quinidine and mefloquine were shown to be high in comparison with the previous study (Bunnag and Harinasuta, 1987).

Whole blood mefloquine concentrations

The mefloquine concentrations on day 4 in patients with and without vomiting are shown in Table 4. It can be seen that patients who vomited had similar mean concentrations with those without vomiting, as most of vomiting occurred after one hour of treatment.

Drug monitoring of mefloquine in patients showed that the concentrations on day 4 from patients with sensitive responses from the western border were lower than those of sensitive responses from the eastern border but similar to mean concentrations obtained from patients with resistant responses who came from the eastern part of Thailand (Fig 1). The concentrations on day 7 of patients with sensitive responses were not different to those with resistant responses. The patients who showed RIII responses had excessive vomiting during the first few hours, mefloquine concentration was found to be 122 ng/ml on day 4.

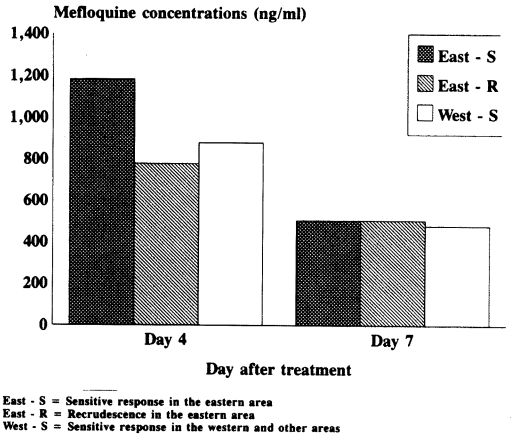

Fig 1—Mefloquine concentrations inpatients with sensitive and resistant response from the western and eastern areas.

DISCUSSION

It has been shown recently that the concentrations of mefloquine on the first two days of treatment in patients with sensitive response were significantly higher than those obtained in patients with recrudescence (Karbwang *et al,* 1991c). Whole blood mefloquine concentrations have been shown to increase when mefloquine was

Table 4

Mean whole blood mefloquine concentration in patients with and without vomiting.

Mefloquine + Tetracycline		MSP + Tetracycline	
Vomiting (n = 8)	Non-vomiting (n = 12)	Vomiting (n = 7)	Non-vomiting (n = 14)
938	1,147	937	1,293

given in the presence of tetracycline (Karbwang *et al,* 1992). The use of tetracycline with mefloquine would be a good combination for treatment of multi-drug resistant falciparum malaria if there is no apparent evidence of adverse effects.

The cure rate obtained with either group was higher than with the standard dose of mefloquine (3 tablets) in the same population *ie* the patients who contracted malaria from the eastern border of Thailand (Rooney 1991, unpublished observation). Even though there was an increase in the cure rate to 75%, this is still not acceptable. The cure rate was, however, similar to that in those received mefloquine 5 tablets in two divided doses (Bunnag 1991, unpublished observation). In order to prevent further spreading of multi-drug resistant falciparum malaria to other areas of the country and neighboring countries, it is therefore essential to have 100% cure rate. Adding tetracycline to mefloquine or MSP increases the cure rate but does not prevent the spreading of drug resistance. This combination seems to be useful in areas where alternative drugs are not available. However, if there are other alternative drugs that offer more than 95% cure rate, then it is reasonable not to use this combination, as taking tetracycline for 7 days would decrease the patient's compliance.

The adverse effects found in this study were mainly of gastrointestinal effects which seems to be higher when compared to the previous studies (Karbwang *et al,* 1991b; Harinasuta *et al,* 1983). Vomiting was found to be 36% and 34% in MSP and mefloquine groups respectively, but most of the vomiting occurred after one hour, thus having little effect on the blood concentration of mefloquine (Table 4). However, one patients who showed an RIII response had a very low mefloquine concentration due to excessive vomiting in the first few hours after treatment. These findings are in agreement with the previous study where early vomiting (*ie* within the first hour) influenced bioavailability of mefloquine but there was no effect in those patients who vomited after one hour (Karbwang *et al,* 1991b).

Mefloquine concentrations in patients with sensitive responses from the western border were statistically lower than those obtained from the eastern border, suggesting that malaria parasites on the eastern border are more resistant to mefloquine and the requirement for mefloquine concentrations to eliminate these parasites must be higher than those in the western and other areas. This is supported by the finding that the concentration in patients with sensitive responses from the western and other areas was similar to that in those with resistant responses on the eastern border.

In vitro sensitivity tests showed that MIC for chloroquine were the same as in the previous study but MIC of mefloquine was higher in this study, suggesting that the mefloquine resistant strains of falciparum are spreading. These data together with requirement of higher mefloquine concentrations to achieve sensitive responses in the eastern border area support this view.

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