TWO DOSES OF ARTEMETHER/MEFLOQUINE OR ARTESUNATE/MEFLOQUINE COMBINATION FOR MULTIDRUG RESISTANT FALCIPARUM MALARIA

Danai Bunnag[1], Tozo Kanda[2], Juntra Karbwang[3], Krongthong Thimasarn[4], Swangjai Pungpak[1] and Tranakchit Harinasuta[3]

[1]Parasitology and Tropical Medicine Association of Thailand; [2]Japan Association for Tropical Medicine; [3]Clinical Pharmacology Unit, Department of Clinical Tropical Medicine and Hospital for Tropical Diseases, Bangkok, Thailand; [4]Malaria Division, Ministry of Public Health, Bangkok, Thailand

Abstract. *Plasmodium falciparum* in Southeast Asia is highly resistant to chloroquine, sulfadoxine/pyrimethamine, quinine and even mefloquine. The use of two doses of short course artemether/mefloquine combination has been shown to be effective in a recent study. In the present study, we have assessed the efficacy of short course treatment with artesunate/mefloquine, in comparison with artemether/mefloquine in patients with multidrug resistant falciparum malaria.

Ninety-nine Thai male patients who sought consultation at Makham Malaria Clinic, Chantaburi (eastern part of Thailand), were randomized to receive either the combination of artemether (150 and 100 mg; group A) or artesunate (150 and 100 mg; group B) with mefloquine (750 and 500 mg) at 24 hours apart. The follow-up was on days 1, 2, 7, 14, 21, 28, 35 and 42. Patients in both groups showed a rapid initial response to treatment; fever and parasite were cleared within 48 hours in 100 and 100% *vs* 91.8 and 96%, for group A *vs* B, respectively. All patients in group A had completed the 42 day-follow up; however, two patients in group B did not finish the 42-day follow-up. The cure rate was 100% in either group. No serious adverse effects were found. Artemether or artesunate with mefloquine given two doses at 24 hours apart can be used as effective alternative treatment regimens for multidrug resistant falciparum malaria.

INTRODUCTION

Plasmodium falciparum in Thailand is highly resistant to chloroquine, sulfadoxine/pyrimethamine, quinine and even mefloquine (Bunnag and Harinasuta, 1987; Bunnag *et al*, 1993; Karbwang and Harinasuta, 1992; Ketrangsee *et al*, 1992; Thimasarn *et al*, 1995). Artemether and artesunate are two artemisinin (qinghaosu) derivatives, which are the most promising antimalarials, currently play an important role in the treatment of uncomplicated and severe, multidrug-resistant falciparum malaria (Bunnag *et al*, 1991; Harinasuta and Karbwang, 1994; Li *et al*, 1994). The action is rapid; more than 90% of parasitemia is cleared within 24 hours. However, recrudescence rate is high with treatment course of shorter than 5 days (Bunnag *et al*, 1991). Short course (30 hours) combination regimen of artemether or artesunate with a long half-life antimalarial such as mefloquine are considered to be highly effective regimens with good patient compliance (Bunnag *et al*, 1995; 1996; Karbwang *et al*, 1995; Na-Bangchang *et al*, 1997). In a more recent study (Bunnag *et al*, 1997), it has been shown that shorter (6 or 24 hour) courses of the combination artemether/mefloquine was very effective with cure rates of 98-100%. As the availability of artemether may be more limited than artesunate in some countries, combination of artesunate with mefloquine can probably be used as an effective alternative regimen if its efficacy has been proven. In the present study, we assessed clinical efficacy of the 24-hour course artesunate/mefloquine, in comparison with artemether/mefloquine in Thai male patients with acute uncomplicated falciparum malaria.

MATERIALS AND METHODS

Ninety-nine Thai patients with acute uncomplicated falciparum malaria (asexual form parasitemia of less than 5%), with no history of liver or kidney diseases, who attended the Malaria Clinic in Makarm district, Chantaburi Province, during 1996 were recruited into the study. They were aged between 15 to 60 years and weighing 45 to 75 kg. Written informed consent for participation to the study was

obtained from all patients. The study was approved by the Ethics Committee of the Ministry of Public Health, Bangkok, Thailand.

The patients were randomly allocated to the following therapeutic regimens;

Group A: 150 mg artemether (Arenco nv, Belgium; 50 mg per tablet) plus 750 mg mefloquine (Lariam®, Hoffman La-Roche, Basel, Switzerland; 250 mg per tablet), followed by 100 mg artemether plus 500 mg mefloquine at 24 hours apart;

Group B: 150 mg artesunate (Guillin Pharmaceutical, China; 50 mg per tablet) plus 750 mg mefloquine, followed by 100 mg artesunate plus 500 mg mefloquine at 24 hours apart. Patients who failed to respond to the treatment were retreated with the same regimen again. These patients were followed up for another 42 days.

Parasite counts were performed on days 0, 1, 2, 7, 14, 21, 28, 35 and 42. The microscopic identification of parasite was done on a thin/thick smear with Giemsa stain, and parasite counts were reported per 1,000 red blood cells or per 200 white blood cells.

All adverse reactions during the study period were recorded with the date and time when they occurred and disappeared. The changes included gastrointestinal, centralnervous, cardiovascular, dermatological and other changes possibly attributable to artemether, artesunate or mefloquine.

The patients were included for efficacy assessment if the follow-up period had been completed to day 42. The efficacy and adverse effects were compared between the two therapeutic regimens. The evaluated parameters were the rapidity of clearing the parasite and fever, and the recrudescence rate. Statistical analysis was done at a significance level of $p = 0.05$, using Fisher's exact test for proportion and the Student's *t*-test for quantitative variables.

RESULTS

Ninety-nine patients with acute uncomplicated falciparum malaria were recruited into the study, 50 in group A and 49 in group B. On admission, all patients presented with fever (100%), 94% had headache, 94% had anorexia, 94% had nausea. No patient had vomiting on admission. Patients' characteristics and levels of admission parasitemia were not statistically significantly different between the two treatment groups (Table 1).

All patients in group A had completed the 42-day follow-up, two patients in group B had the last follow-up on days 14 and 28, thus they were excluded from the efficacy analysis. Patients in either group had a rapid initial response; 100 and 96% of patients in group A and B, respectively cleared the parasitemia within 48 hours after treatment. The fever was cleared within 48 hours in all patients in group A and 91.8% of patients in group B. None had reappearance of the parasitemia during 42-days follow-up period; the cure rates were 100% in either group (95% C.I. = 1-1) (Table 2).

Vomiting, anorexia and diarrhea were found in both groups at equal distribution; however, the symptoms were mild and transient which required no specific treatment. No neuropsychiatric adverse effect was observed in any patient during the 42 day follow-up period. No patient developed *P. vivax* malaria during the follow-up period.

Table 1

Admission clinical and laboratory data, presented as mean (SD).

	Artemether/mefloquine (N = 50)	Artesunate/mefloquine (N = 49)
Age (years)	31.5 (10.7)	30.5 (11.1)
Weight (kg)	53.7 (5.9)	54.4 (49)
Temperature (°C)	38.4 (0.85)	38.5 (0.8)
Parasitemia (/μl)*	12,535 (600-220,000)	6,660 (360-226,800)

* geometric mean (range)

Table 2

Therapeutic responses.

	Artemether/mefloquine (N = 50)	Artesunate/mefloquine (N = 49)
FCT (h) (N, %):		
within 24 hours	40 (80)	36 (73.5)
within 24-48 hours	10 (20)	9 (18.4)
not clear at 48 hours	0 (0)	4 (8.2)
PCT (h) (N, %):		
within 24 hours	49 (98)	35 (71.4)
within 24-48 hours	1 (2)	12 (24.5)
not clear at 48 hours	0 (0)	2 (4.1)
Evaluable number (N)	50	47
Cure rate (%)	100	100
S response (N)	50	47
S/RI response (N)	0	2
RI response (N)	0	0
P. vivax (N)	0	0

DISCUSSION

High efficacy (cure rate of 97-98%) of a single oral dose (300 mg) artemether or artesunate, followed by mefloquine (1,250 mg) as two divided doses on the following day (24 and 30 hours after the initial dose), has previously been shown in multidrug resistant falciparum malaria, with rapid clearance of parasite and fever (Bunnag *et al*, 1995; 1996; Karbwang *et al*, 1995). Although the compliance of the patients was shown to be good (Na-Bangchang *et al*, 1997), shorter duration of treatment may be more favorable, particularly when using outside hospital settings. Despite the evidence suggestive of high and comparable clinical efficacy of the two shorter course regimens of artemether/mefloquine (given as two doses at 6 or 24 hours interval) from our previous study (Bunnag *et al*, 1997), the regimen which combination drugs are given at 24 hours apart was chosen for investigation in the present study. It is likely that the period of 24 hours should produce less side-effects, since aggravating symptoms from malaria are expected to be less on the second day.

We have shown that the efficacy of the combination of artesunate/mefloquine, given at the same doses was equally effective as that of artemether/mefloquine combination regimen. The parasites and fever were cleared rapidly with either tested regimen. The cure rate of 100% obtained from both regimens suggests that these combination regimens can be used for treatment, as well as stand-by drug in the areas of multidrug-resistant falciparum malaria. Furthermore, as the previous study (Bunnag *et al*, 1997) was carried out two years prior to the present study, this finding does point out that the parasites have not yet developed resistance to this combination. The efficacy of the combination of these two regimens is as effective as that of the sequential regimen (Bunnag *et al*, 1995; 1996; Karbwang *et al*, 1995), and therefore, providing additional two alternative regimens for multidrug resistant falciparum malaria. Formulation of these two drugs as a fixed combination may be proposed to make it more convenient for the patients. Although there were reports on the kinetic drug interaction between artesunate/artemether and mefloquine (Karbwang *et al*, 1994), giving two doses of artesunate/artemether overrides the kinetic antagonistic interaction which results in lower mefloquine level. The observation that the combination artesunate/mefloquine and artemether/mefloquine are equally effective, is rather unanticipated in view of kinetic characteristics of artesunate and artemether. Although systemic availability of artesunate and its active plasma metabolite – dihydroartemisinin is much greater than that of oral artemether (Karbwang *et al*, 1997a; 1997b), their duration of systemic exposure is shorter (within 6 hours after dosing). Since the development of malaria parasites is dynamic, suppression of parasites' development throughout 24 hours is essential, especially during

the acute phase infection. By giving mefloquine concurrently with an initial dose of artesunate, period of non-suppression between artesunate dose is therefore off set by the presence of mefloquine concentration in plasma (which has much longer residence time in the body).

In conclusion, combination of either artemether or artesunate with mefloqine as two doses regimen at 24 hours apart can be considered as alternative effective treatment regimens in areas with multidrug resistant falciparum malaria. These regimens can be considered more preferable than the sequential short course regimens of artemether or artesunate, followed by mefloquine on the following day. The total dose of artesunate/artemether used is lower (250 *vs* 300 mg) and the duration of treatment is shorter (24 *vs* 30 hours). These regimens can be used as possible stand-by treatments for those patients who visit malaria endemic areas longer than a week and suffer from fever, headache, with or without anorexia/vomiting.

ACKNOWLEDGEMENTS

The study was supported mainly by Japanese Ministry of Posts and Telecommunications, Japan. We are grateful to the staff of Makham Malaria Clinic, Chantaburi Province, for their excellent assistance. Artemether was supplied by Arenco Co Ltd, Artesunate and Lariam was kindly provided by Malaria Division, Ministry of Public Health, Thailand. JK is supported by National Science and Technology Development Agency (NSTDA) of Thailand.

REFERENCES

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

Bunnag D, Viravan C, Karbwang J, *et al*. Clinical trials with halofantrine in acute uncomplicated falciparum malaria in Thailand. *Southeast Asian J Trop Med Public Health* 1993; 24 : 43-8.

Bunnag D, Viravan C, Looareesuwan S, Karbwang J, Harinasuta T. Double blind randomised clinical trial of two different regimens of oral artesunate in falciparum malaria. *Southeast Asian J Trop Med Public Health* 1991; 22 : 534-8.

Bunnag D, Kanda T, Karbwang J, Thimasarn K, Pungpak S, Harinasuta T. Artemether or artesunate followed by mef.oquine as a possible treatment for multidrug resistant falciparum malaria. *Trans R Soc Trop Med Hyg* 1996; 90 : 415-7.

Bunnag D, Kanda T, Karbwang J, Thimasarn K, Pungpak S, Harinasuta T. Artemether-mefloquine combination in multidrug resistant falciparum malaria. *Trans R Soc Trop Med Hyg* 1995; 89 : 213-5.

Bunnag D, Kanda T, Karbwang J, Thimasarn K, Pungpak S, Harinasuta T. Artemether/mefloquine combination for multidrug resistant falciparum malaria. *J Trop Med Parasitol* 1997; 20 : 21-4.

Harinasuta T, Karbwang J. [Edition]. Qinghaosu: A promising antimalarial. *JAMA SEA* 1994; 22 : 7-8.

Karbwang J, Harinasuta T. Distribution of drug resistance. In: Karbwang J, Harinasuta T, eds. Chemotherapy of Malaria in Southeast Asia. Bangkok: Roumtassana Press 1992: 47-72.

Karbwang J, Na-Bangchang K, Thanavibul A, Back DJ, Bunnag D, Harinasuta T. Pharmacokinetics of mefloquine alone or in combination with artesunate. *Bull WHO* 1994; 72 : 83-7.

Karbwang J, Na-Bangchang K, Congpoung K, Molunto P, Thanavibul A. Pharmacokinetics and bioavailability of oral and intramuscular artemether. *Eur J Clin Pharmacol* 1997a; 52 : 307-10.

Karbwang J, Na-Bangchang K, Congpoung K, Thanavibul A, Harinasuta T. Pharmacokinetics of oral artesunate in Thai patients with uncomplicated falciparum malaria. *Clin Drug Invest* 1998; 15 : 37-43.

Karbwang J, Na-Bangchang K, Thanavobul A, Ditta-in M, Harinasuta T. A comparative trial of two different regimens of artemether plus mefloquine in multidrug resistant falciparum malaria. *Trans R Soc Trop Med Hyg* 1995; 89 : 296-8.

Ketrangsee S, Vijayakadga S, Yamokgul P, Jatapadma S, Thimasarn K, Rooney W. Comparative trial on the response of *Plasmodium falciparum* to halofantrine and mefloquine in Trat Province, Eastern Thailand. *Southeast Asian J Trop Med Public Health* 1992; 23 : 55-8.

Li GQ Guo XB, Fu LC, Jian HX, Wang XH. Clinical trials of artemisinin and its derivatives in the treatment of malaria in China. *Trans R Soc trop Med Hyg* 1994; 88 (suppl 1): 5-6.

Thimasarn K, Sirichaisinthop J, Vijayakadga S, *et al*. *In vivo* study of the response of *Plasmodium falciparum* to standard mefloquine/sulfadoxine/pyrimethamine (MSP) treatment among gem-miners returning from Cambodia. *Southeast Asian J Trop Med Public Health* 1995; 26 : 204-12.

Na-Bangchang K, Congpoung K, Sirichaisinthop J, Suprakorb K, Na-Bangchang K. Compliance with a 2 day course of artemether-mefloquine in an area of highly multi-drug resistant *Plasmodium falciparum* malaria. *Br J Clin Pharmacol* 1997; 43 : 639-42.