MONITORING THE THERAPEUTIC EFFICACY OF ANTIMALARIALS AGAINST UNCOMPLICATED FALCIPARUM MALARIA IN THAILAND

C Rojanawatsirivej[1], S Vijaykadga[1], I Amklad[1], P Wilairatna[2] and S Looareesuwan[2]

[1]Malaria Division, Ministry of Public Health, Nonthaburi; [2]Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

Abstract. Increasing antimalarial drug-resistance is an important problem in Thailand. The results of monitoring the antimalarial efficacy are used in decision-making about using antimalarials to treat uncomplicated falciparum malaria in Thailand. In 2002, 552 patients with uncomplicated malaria were treated according to the Thai National Drug Policy, with mefloquine 25 mg/kg plus artesunate 12 mg/kg and primaquine 30 mg in divided doses for 2 days in high-mefloquine-resistant areas; mefloquine 15 mg/kg plus primaquine 30 mg in non- or low-mefloquine-resistant areas; mefloquine 15 mg/kg plus artesunate 12 mg/kg and primaquine 30 mg in divided doses for 2 days or Coartem® (6-dose regimen for adult contains 480 mg artemether and 2880 mg lumefantrine) plus primaquine 30 mg given over 3 days in moderate-mefloquine-resistant areas. The study shows that mefloquine, artesunate plus mefloquine, and artemether plus lumefantrine are effective in the treatment of uncomplicated malaria in most areas of Thailand except for Ranong and Kanchanaburi, where the first-line treatment regimen should be revised.

INTRODUCTION

Antimalarial resistance has spread and intensified in Thailand over the past 40 years. There is now a very high level of drug resistance, with evidence both *in vitro* and *in vivo* of *P. falciparum* parasites that are highly resistant to chloroquine, sulfadoxine-pyrimethamine, mefloquine and quinine (Looareesuwan *et al*, 1992; Thimasarn *et al*, 1997). The increasing resistance of *P. falciparum* to mefloquine led to the addition of artesunate to the routine treatment of malaria cases in Trat, Chantaburi, Sa Kaeo, (Thai/Cambodian border) and Tak (Thai/Myanmar border). Resistance of *P. falciparum* to antimalarials is a major contributing factor to the deterioration in malaria control.

In the face of increasing resistance by *P. falciparum* to most antimalarials, monitoring drug efficacy may facilitate decision-making about the use of antimalarials for treating uncomplicated falciparum malaria (WHO, 1994; 1997; 2001).

The purpose of this study was to ascertain the therapeutic efficacy of first-line treatment for uncomplicated falciparum malaria in Mae Hong Son (MHS), Tak (TK), Kanchanaburi (KB), Ratchaburi (RB), Ranong (RN), (Thai-Myanmar border), Ubon Ratchathani (UB), Chanthaburi (CHB) and Trat (TR) (Thai-Cambodian border) with a view to updating the existing National Antimalarial Drug Policy.

MATERIALS AND METHODS

The study was carried out in the malaria clinics of MHS, TK, KB, RB, RN (Thai-Myanmar border) and UB, TR and CHB (Thai-Cambodian border), in 2002. The study areas were characterized by endemic and seasonal forest-related malaria; *Anopheles minimus* and *An. dirus* are the principal vectors. The prevalent parasite species were *P. falciparum* and *P. vivax* (1:1). Resistance to chloroquine and sulfadoxine-pyrimethamine (S-P) was complete in these areas. Mefloquine resistance was reported in TK, CHB and TR.

Study design

A total of 552 patients with symptomatic

Correspondence: P Wilairatna, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand.
Tel: 66 (0) 2248-3188 Ext 1624; Fax: 66 (0)
E-mail: dirctm@mucc.mahidol.ac.th

microscopically-confirmed falciparum malaria were recruited into the study. After giving written informed consent, they were assigned to receive the first regimens depending on the area, according to the National Drug Policy described below:

• high-mefloquine-resistant areas (TK, TR and CHB): mefloquine 25 mg/kg (Mephaquin®, Mepha Ltd, Aesch-Basle, Switzerland) plus artesunate 12 mg/kg (Artesunate®, Guilin Pharmaceutical Works, Guangxi, China) and primaquine 30 mg in divided doses for two days;

• non- or low-mefloquine-resistant areas (CH, MHS, KB, RB, RN and UB): mefloquine 15 mg/kg plus primaquine 30 mg single dose;

• moderate-mefloquine-resistant areas: two more regimens were included: mefloquine 15 mg/kg plus artesunate 12 mg/kg and primaquine 30 mg in divided doses for two days in KB; or Coartem® (20 mg of artemether and 120 mg of lumefantrine per tablet; Novartis, Basel, Switzerland.) plus primaquine 30 mg in RB. The dosage for adult ≥35 kg was four tablets per dose, with a 6-dose regimen given over three days at 0, 8, 24, 36, 48 and 60 hours.

Thick blood smears by Giemsa were taken to detect malaria parasites from the patients. The number of parasites per 200 leukocytes was multiplied by 40 to give the count per microliter.

On enrolment (day 0), study subjects' parasite density and body temperature were recorded along with any other symptoms and signs. Follow-up examinations were scheduled on days 1, 2, 3, 7, 14, 21 and 28 after the start of treatment. Body temperature and parasite density were measured on each of these days, and the parasite density ratios on days 2 and 3, to that on day 0, were calculated. In addition, patients could return at any time if their condition worsened, and body temperature and parasite density were measured at each unscheduled visit. If at any of the follow-up visits, patients were febrile (axillary temperature ≥ 37.5ºC) and had parasitemia, and no other causes of fever were found, an alternative malaria treatment was given, and the case was classified according to the WHO classification system (2000), as described below (WHO, 1997; WHO 2001):

Clinical and parasitological response

Early treatment failure (ETF). Development of danger signs or severe malaria on day 1, day 2 or day 3, in the presence of parasitemia; parasitemia on day 2 higher than day 0 count; parasitemia on day 3 with axillary temperature ≥ 37.5ºC; parasitemia on day 3 ≥ 25% of count on day 0.

Late treatment failure (LTF). Development of danger signs or severe malaria after day 3, in the presence of parasitemia; unscheduled return of the patient because of clinical deterioration (including fever), in the presence of parasitemia; presence of parasitemia on any of the scheduled returns, on day 7, day 14, day 21, or day 28 (same species as on day 0).

Adequate clinical response (ACR). Absence of parasitemia on day 28 without previously meeting any of the criteria of early or late treatment failures.

Statistical analysis

Data were analyzed using the statistical package SPSS for Windows (SPSS Software, Gorinchem, The Netherlands). Proportions were compared using χ^2 and Fisher's exact test. Rate ratio (RR) and Taylor series 95% confidence limits were also calculated.

RESULTS

A total of 552 child and adult patients aged 10-74 years, with acute uncomplicated falciparum malaria, were selected for the study. Acute uncomplicated falciparum malaria was defined as an asexual parasitemia between a minimum of 80 parasites/μl and a maximum of 200,760 parasites/μl and fever (axillary temperature ≥37.5ºC) or a history of fever within the previous 48 hours. Twenty patients (3.6%) did not complete follow-up. Clinical data and baseline laboratory investigations on day 0 (Table 1) were compared for the mefloquine, mefloquine-plus-artesunate and Coartem® (artemether plus lumefantrine) groups.

Clinical and parasitological response (Fig 1)

Mefloquine. Of 318 patients, 5 (1.6%) did not complete follow-up; 1 patient was lost to follow-up on day 3, and 4 patients on days 14-21.

Table 1
Baseline data for the study patients.

Regimen/provinces	No. of patients	Mean age (years)	Mean weight (kg)	Mean body temperature (ºC)	Geometric mean parasitemia (per μl)
Mefloquine 15 mg/kg + Primaquine 30 mg					
Mae Hong Son	57	30.79 (15-65)	54.69 (38-84)	38.38 (36.00-41.00)	12,120.70 (240-120,000)
Kanchanaburi	109	30.96 (10-68)	53.67 (40-95)	38.42 (36.60-40.30)	25,491.01 (600-200,760)
Ratchaburi	80	34.51 (12-73)	53.92 (35-81)	38.10 (36.00-40.50)	12,026.50 (80-72480)
Ranong	42	33.31 (15-58)	55.19 (40-72)	39.13 (37.90-41.00)	11,412.38 (680-72,000)
Ubon Ratchathani	30	35.67 (17-60)	54.97 (40-83)	38.50 (36.50-40.70)	28,974.67 (1,000-72,000)
Mefloquine 25 mg/kg + Artesunate 12 mg/kg + Primaquine 30 mg					
Tak	43	31.42 (15-53)	57.23 (43-92)	38.52 (36.61 -40.00)	12,350.70 (2,440-80,000)
Chantaburi	38	33.39 (14-68)	53.50 (42-73)	38.90 (37.00-41.00)	24,723.16 (280-140,000)
Trat	72	36.33 (10-74)	55.06 (36-75)	38.61 (36.00-41.00)	17,858.89 (1,640-76,800)
Mefloquine 15 mg /kg+ Artesunate 12 mg/kg + Primaquine 30 mg					
Kanchanaburi	46	29.54 (12-65)	55.52 (40-75)	37.93 (36.30-40.00)	14,906.09 (720-65,600)
Coartem® (6-dose regimen) + Primaquine 30 mg					
Ratchaburi	33	33.03 (13-66)	55.21 (40-78)	38.25 (36.00-40.10)	5,578.18 (240-26,680)

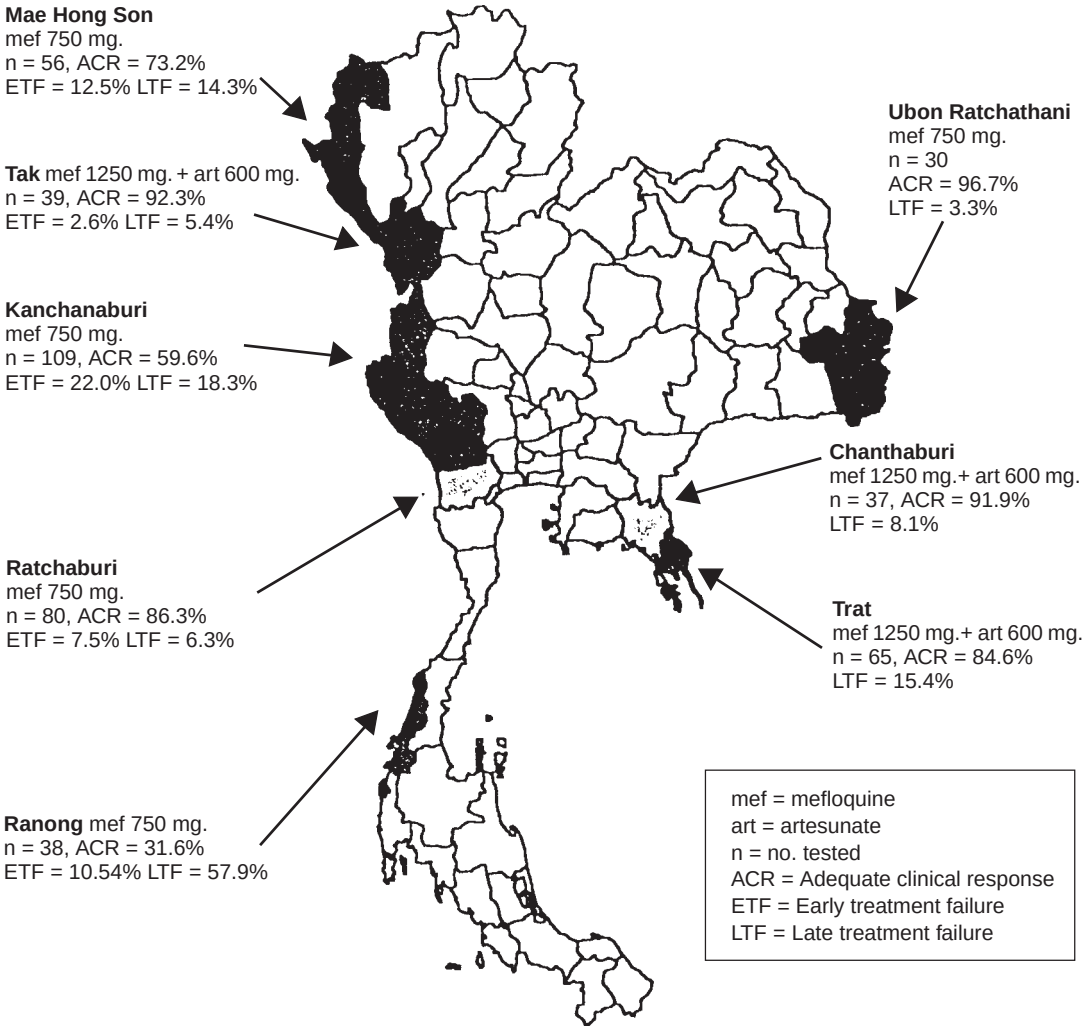
The adequate clinical response was highest in UB (96.7%) and the lowest in RN (31.6%). Ninety-seven (31%) patients were classified as treatment failures: 56 late-treatment failures and 41 early-treatment failures (Table 2).

Among the patients classified as late-treatment failures, 3, 12, 10, 16 and 18 tested positive on days 7, 14, 21 and 28, respectively.

Mefloquine 25 mg/kg plus artesunate 12 mg/kg. Out of 153 patients, 12 (7.8%) did not complete follow-up. The adequate clinical response was highest in CHB (91.9%), and lowest in TR (84.6%). Among the patients classified as late-treatment failures, 2, 6 and 9 tested positive on days 14, 21 and 28, respectively.

Mefloquine 15 mg/kg plus artesunate 12 mg/kg. Out of 46 patients, 1 (2.2%) did not complete follow-up. The adequate clinical response was 39 (86.7%). Of the patients classified as early-treatment failures, 4 (8.9%) had worsened clinical conditions on day 1; and 1 patient was positive for parasitemia on day 3, with an axillary temperature ≥37.5ºC. Two patients were classified as late-treatment failures; 1 tested positive on day 14 and the other was positive on day 28.

Coartem®. All 33 (100%) patients were classified with adequate clinical response (Table 2).



DISCUSSION

This study demonstrated mefloquine resistance in Ranong, Kanchanaburi and Mae Hong Son. Antimalarial resistance might spread between Thailand and Myanmar more than up to Tak and Mae Hong Son down to Kanchanaburi or Ranong because there was greater population migration between the two countries than among the provinces. More data should be gathered in Myanmar opposite Ranong, Kanchanaburi and Mae Hong Son.

Ranong is a province in the south of Thailand close to Thai-Myanmar border. It is far from Kanchanaburi and Mae Hong Son. There is less population migration among the provinces than between the two countries. The mefloquine cure rates in RN have been decreasing in the years 1997, 1998, 1999 and 2000 to 96%, 81%, 38%, and 31%, respectively (Malaria Division, 2002a). In 2002, the rates in ACR, ETF and LTF were 31%, 10.5% and 57.9%, respectively (Malaria Division, 2002b). Reappearances of parasitemia on days 3, 7, 14, 21 and 28 were observed in 4, 2, 6, 8 and 7 patients, respectively. Thus the national antimalarial drug program should be revised.

There was also mefloquine resistance in Kanchanaburi. ACR had decreased from 82% in 1997 to 59.6% in 2002. At the end of this study, the national antimalarial program was changed

Table 2
Clinical and parasitological response of uncomplicated falciparum malaria to different antimalarial regimens in Thailand, 2002.

Regimen/ Provinces	Early treatment failure (%)	Late treatment failure (%)	Adequate clinical response (%)	Total (%)
Mefloquine 15mg/kg + Primaquine 30 mg				
Mae Hong Son	7 (12.5)	8 (14.3)	41 (73.2)	56 (100)
Kanchanaburi	24 (22.0)	20 (18.3)	65 (59.6)	109 (100)
Ratchaburi	6 (7.5)	5 (6.3)	69 (86.3)	80 (100)
Ranong	4 (10.5)	22 (57.9)	12 (31.6)	38 (100)
Ubon Ratchathani	-	1 (3.3)	29 (96.7)	30 (100)
Total	41(13.1)	56 (17.9)	216 (69.0)	313 (100)
Mefloquine 25mg/kg + Artesunate 12 mg/kg + Primaquine 30 mg				
Tak	1 (2.6)	2 (5.4)	36 (92.3)	39 (100)
Chantaburi	-	3 (8.1)	34 (91.9)	37 (100)
Trat	-	10 (15.4)	55 (84.6)	65 (100)
Total	1 (0.7)	15 (10.6)	125 (88.6)	141 (100)
Mefloquine 15 mg/kg + Artesunate 12 mg/kg + Primaquine 30 mg				
Kanchanaburi	4 (8.9)	2 (4.4)	39 (86.7)	45 (100)
Total	4 (8.9)	2 (4.4)	39 (86.7)	45 (100)
Coartem® + Primaquine 30 mg				
Ratchaburi	-	-	33 (100)	33 (100)
Total	-	-	33 (100)	33 (100)

from mefloquine alone to mefloquine 15 mg/kg plus artesunate 12 mg/kg. After the antimalarial drug regimen was amended, the ACR was 86.7%. The rather low ACR may be attributed to the adverse side-effects of the drugs. Four patients were referred to hospital. If these 4 patients were excluded from the study, the ACR would be higher (95.1%).

The ACR for the mefloquine-artesunate combination regimen in Tak, Chantaburi and Trat were 92.3%, 91.9% and 84.6%, respectively (Malaria Division, 2002a). The ACR in Trat, in 1997, 1998 and 2002 decreased, from 93%, 92.5% to 84.6%, respectively. The clinical responses of the drugs were similar to *in vitro* results: there was higher mefloquine resistance in Trat than in Tak (EC_{50}: Tak = 736.35 n mol/1, Trat = 1,684 n mol/l; EC_{90}: Tak = 3,006.5 n mol/l: Trat = 9,630.5 nmol/l). It was interesting to consider the factors that may have contributed to the greater drug resistance in Trat. Although the ACR in Chantaburi, close to Trat, was 92.3%, which was higher than Trat, no significant difference in ACR was noted.

An efficacy study was also conducted in a new area in Ratchaburi, close to Kanchanaburi and Myanmar. The ACR for mefloquine 15 mg/kg was 86.3%. The new antimalarial, Coartem®, was registered for use in Thailand in 2001, after the efficacy study (90-100%) was carried out at the Bangkok Hospital for Tropical Diseases, Thailand (Wilairatana *et al*, 2001). A six-dose regimen of Coartem® given over 3 days showed efficacies of 97-99 % (van Vugt *et al*, 1999). This six-dose regimen study in Ratchaburi showed an ACR of 100% (n=33).

In conclusion, mefloquine alone; mefloquine plus artesunate; and Coartem® were effective in the treatment of uncomplicated malaria in most areas of Thailand in 2002, except for Ranong and Kanchanaburi, where mefloquine alone was the first line treatment regimen. This regimen should be changed as soon as possible.

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REFERENCES

Malaria Division. Annual report of fiscal year 2001. Bangkok: Veteran Organization Press, 2002a: 39-43.

Malaria Division. Country report on malaria control programme in Thailand. Paper presented at Bi-regional (SEAR/WPR) Workshop on Situation Assessment and Monitoring for Roll Back Malaria in Southeast Asia. Manila, Philippines: WHO, 2002b.

Looareesuwan S, Viravan C, Vanijanonta S, *et al*. Randomised trial of artesunate and mefloquine alone and in sequence for acute uncomplicated falciparum malaria. *Lancet* 1992; I: 821-4.

Thimasarn K, Sirichaisinthop J, Chanyakhun P, *et al*. A comparative study of artesunate and artemether in combination with mefloquine on multidrug resistant falciparum malaria in eastern Thailand. *Southeast Asian J Trop Med Public Health* 1997; 28: 465-71.

van Vugt M, Wilairatana P, Gemperli B, *et al*. Efficacy of six doses of artemether-lumefantrine (benflumetol) in the treatment of multi-drug resistant falciparum malaria. *Am J Trop Med Hyg* 1999; 60: 936-42.

Wilairatana P, Krudsood S, Silachamroon U, *et al*. Pharmaco-epidemiology of artemisinin derivatives in Bangkok Hospital for Tropical Diseases. *Intern Med J Thai* 2001; 17: 253-8.

WHO. Antimalarial drug policies: data requirements, treatment of uncomplicated malaria, and management of malaria in pregnancy. Report of an informal consultation, 14-18 March, 1994.

WHO. Assessment of therapeutic efficacy of antimalarial drugs for uncomplicated falciparum malaria [Draft 28.2.97], 1997.

WHO. Monitoring antimalarial drug resistance. Report of a WHO consultation. Geneva, Switzerland: WHO, 3-5 December, 2001.