ASSESSMENT OF THERAPEUTIC EFFICACY OF CHLOROQUINE FOR VIVAX MALARIA IN THAILAND

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Abstract. Chloroquine-resistant *Plasmodium vivax* has been reported in some Asian countries. In 2003, 161 patients infected with vivax malaria were treated according to the Thai National Drug Policy, with oral chloroquine (approximately 25 mg base/kg body weight, administered over 3 days) followed by primaquine on day 28 (15 mg daily for 14 days). All the patients were initially cured after chloroquine treatment, clearing their parasitemias within 7 days. Only one patient presented with parasitemia at 28 days. These data indicate that chloroquine is still effective for the treatment of patients with vivax malaria in Thailand.

INTRODUCTION

In Thailand, malaria is still a public health problem. *Plasmodium falciparum* and *P. vivax* are the main species representing 49% and 51% of all infected cases, respectively. Thailand is faced with multi-drug resistant falciparum malaria along the Thai-Myanmar and Thai-Cambodian borders. In response to this situation, Thailand has carried out a program for monitoring drug resistance in *Plasmodium falciparum* since the year 1978. The Malaria Control Program conducts annual therapeutic efficacy evaluations and assessments of the response of *Plasmodium falciparum* to antimalarial drugs. The data collected are used to update the existing National Antimalarial Drug Policy.

Chloroquine, a cheap and widely available antimalarial agent, has been the treatment of choice for the past 50 years for *P. vivax* malaria in Thailand (Purittakamee *et al*, 2000). Recently chloroquine resistant *P. vivax* has been reported in several countries; including Papua New Guinea (Rickmann *et al*, 1989; Schuurkamp *et al*, 1992), Indonesia (Baird *et al*, 1991; 1997; Fryauff *et al*,1998; Sumawinata *et al*, 2003), Myanmar (Myat-Phone-Kwyaw *et al*, 1993; Marlar-Than *et al*, 1995), India (Garg *et al*, 1995; Dua *et al*, 1996), and Guiyana (Phillips *et al*, 1996), but no resistance has been reported in areas with high levels of *P. falciparum* drug resistance, such as in Thailand. (Looareesuwan *et al*, 1999; Pukrittayakamee *et al*, 2000; Congpuong *et al*, 2002).

Since 1997, vivax malaria has emerged in many parts of the country. The falciparum/vivax ratio changed from 1.1:1 in 1999 to 0.8:1 in 2000. Different reasons can explain the increased incidence of vivax malaria: effective treatment of falciparum malaria with artesunate and mefloquine, possible changes in anopheline fauna or possible *P. vivax* resistance to chloroquine. The purpose of this study was to monitor the therapeutic efficacy of chloroquine for vivax malaria in Thailand.

MATERIALS AND METHODS

A total of 161 male and female (non-pregnant) patients, over a 10 year period, with symptomatic vivax malaria, microscopically confirmed, were recruited into the study. The exclusion criteria were infection with other *Plasmodium* species or mixed infection, the presence of a clinical condition requiring hospitalization and the history of antimalarial treatment during the past 4 weeks. After informed consent, the patients received chloroquine 1,500 mg base given over

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3 days (300 mg, three times, at 6-hourly intervals, on the 1st day, followed by 300 mg daily for the next 2 days). This study aimed at determining the failure rate of chloroquine alone, since full course administration of primaquine 15 mg base once daily for 14 days was postponed to day 28.

On enrollment (Day 0), the study subjects' parasite density and body temperature were recorded along with any other symptoms and signs. Clinical examinations, including axillary temperature, were conducted on Days 1, 2, 3, 7, 14, 21, and 28 and parasitological examination was conducted on Days 2, 3, 7, 14, 21, and 28. In addition, patients could return at any time if their condition worsened. Body temperature and parasite density were monitored at each unscheduled visit. Treatment failure (TF) was defined according to the WHO classification (WHO, 2001):

Clinical deterioration due to *P. vivax* illness requiring hospitalization in the presence of parasitemia.

The presence of parasitemia and an axillary temperature ≥ 37.5ºC at any time between Day 3 and Day 28.

The presence of parasitemia on any day between Day 7 and Day 28, irrespective of the clinical condition.

All patients classified as failures received rescue treatment.

This study was approved by the Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Thailand.

Statistical analysis

Data were analyzed using the WHO-program. Proportions were compared using χ^2 and Fisher's exact tests. Rate ratios (RR) and Taylor series 95% confidence limits were also calculated.

RESULTS

A total of 161 patients with uncomplicated vivax malaria (130 males and 31 females) from Sakaeo, Ranong, and Yala Provinces were included in the study. Ten patients (6.2%) did not complete the follow-up. Clinical and parasitological parameters are shown in Table 1. The efficacies of chloroquine for the treatment of vivax patients in Sakaeo, Ranong, and Yala Provinces were 100%, 98.1%, and 100%, respectively. There was only one recrudescence on Day 28 after drug administration.

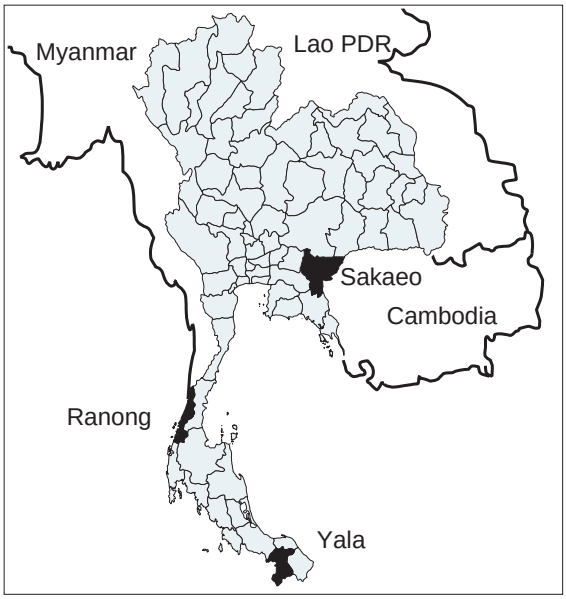

Fig 1- Study sites in Thailand.

DISCUSSION

According to the Thai National Drug Policy, the first line regimen for vivax malaria is chloroquine 1,500 mg base given over 3 days plus primaquine 15 mg base given for 14 days. This study aimed at determining the failure rate of chloroquine alone. Primaquine was given at the termination of the protocol (Day 28). The results of this study indicated that there was no sign of chloroquine-resistant *P. vivax* in Sakaeo, Ranong, and Yala. The treatment success rate was 98.1%. Only one patient failed on Day 28. Chloroquine concentration was not performed, but this case was likely due to a relapse (Baird *et al*, 1997).

The geographical features of the three provinces are obviously different. The results of the study were evaluted for each province. Sakeao is a province in the Southeastern part of Thailand, close to Thai-Cambodian border. Since 1997, the incidence of malaria in this province has increased significantly (Ketkaew *et al*, 1998). The total number of malaria cases in 1995 were 666, and in 1997 were 4,381. In the past, the incidence of

Table 1
Baseline data for the malaria patients.

Provinces	No. of patients	Gender		Mean age (years) (range)	Mean weight (range) (kg)	Mean body temperature (°C) (range)	Parasitemia (per μl) (Geometric mean)
		Male	Female				
Sakaeo	50	49	1	37.0 (17-64)	60.2 (35-75)	38.2 (36.3-42.0)	9,658 (600-66,880)
Ranong	61	47	14	32.2 (11-84)	56.3 (32-85)	38.8 (37.0-41.0)	3,857 (440-30,120)
Yala	50	34	16	27.6 (11-62)	52.2 (25-88)	37.8 (36.0-40.5)	8,198 (200-80,000)
Total	161	130	31				
Average (range)				32.3 (11-84)	56.2 (25-88)	38.3 (36.0-42.0)	7,000 (200-80,000)

Table 2
Clinical and parasitological responses of vivax malaria to chloroquine in Thailand in 2003.

Provinces	Loss (%)	TF (%)	TS (%)	Total (%)
Sakaeo	2 (4.0)	0 (0)	48 (100)	50 (100)
Ranong	8 (13.1)	1 (1.9)	52 (98.1)	61 (100)
Yala	0 (0)	0 (0)	50 (100)	50 (100)
Total	10 (6.2)	1 (0.7)	150 (99.3)	161 (100)

TF=treatment failure; TS=treatment success.

falciparum malaria was higher than the incidence of vivax malaria. In 1997, the ratio of *P. falciparum* to *P. vivax* changed to a preponderance of *P. vivax*. This event corresponded to an increase immigration to Thailand of Cambodian agricultural laborers. From entomological investigations, only *An. barbirostris* and *An. campestris* were found in this area, despite *An. minimus* and *An. dirus* being the principle vectors in Thailand. Although no sporozoites were detected in the salivary glands of those collected mosquitos, they were suspected to be the malaria vectors. Drug resistance surveillance, both *in vivo* and *in vitro*, found that chloroquine was still a very effective treatment for vivax malaria in Sakaeo (Congpoung *et al*, 2002).

Ranong is located in the southern part of Thailand, on the border of Myanmar. Some part of this province is costal area. The major occupations in this province are woodcutting, fishery and tin mining. Occupational migration is common among this local population. Some Burmese have come to Thailand to be employees in fisheries, the tin mining industries, and others. Thais also cross into Myanmar for timber and trading. These movements across the border have an impact on malaria transmission. Ranong is one of nine falciparum malaria sentinel sites in Thailand.

Recently, *P. falciparum* showed a poor response to mefloquine, both *in vitro* and *in vivo*. In 2000, the efficacy of mefloquine alone (750 mg) was 81%, but this decreased to 38% and 31.8% in 2001 and 2002, respectively. To respond to this situation, the Thai Malaria Control Program changed it's recommendation for first-line therapy from monotherapy with mefloquine (750 mg) to mefloquine 1,250 mg in combination with artesunate 600 mg in divide doses for 2 days. (Rojanawatsirivet and Vijaykadga, 2003). The incidence of vivax malaria in this province is usually higher than the incidence of falciparum malaria. An evaluation of the therapeutic efficacy of choroquine for vivax malaria in Ranong was con-

ducted for first time. The results showed that only one patient had recrudescence on Day 28.

Yala is a province in the South of Thailand, close to Malaysia. This area is forested. *An. maculatus, An. minimus,* and *An. dirus* are the main vectors. The main occupations are rubber production and raising song-birds. Vector control by insecticide spraying is difficult because of the bird raising in this area. Hence malaria transmission continues to occur in this area. Rubber workers are prone to mosquito bites, since they work at dawn. Single-dose mefloquine is still the treatment of choice for *P. falciparum* in Yala, whereas a combination of mefloquine and artesunate have been adopted for treatment in Sakaeo and Ranong. Since 2000, the incidence of vivax malaria in this area has increased. However, *P. vivax* still responds well to chloroquine.

In summary, there is no evidence of chloroquine resistance to *P. vivax* in Thailand. This study supports earlier findings (Looareesuwan *et al*, 1999; Congpuong *et al*, 2002) that chloroquine-resistant *P. vivax* is rare or absent in Thailand, since most *P. vivax* isolates remain sensitive and respond well to chloroquine. Although chloroquine is effective, there is a need for regular monitoring of the therapeutic efficacy of chloroquine against *P. vivax* malaria in Thailand, as an early warning system.

ACKNOWLEDGEMENTS

We thank the malaria clinic staff who devoted their time contributing to the most important part of the study. We also thank the microscopists in the Bureau of Vector-borne Diseases for checking the blood films; Pascal Ringwald, Dr Danai Bunnag, and Dr Krongthong Thimarsarn for their advice. This study was supported by the World Health Organization (SE/02/254154) and a Mahidol University Research Grant.

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