MEFLOQUINE – ITS 20 YEARS IN THE THAI MALARIA CONTROL PROGRAM

Chansuda Wongsrichanalai[1], Somsak Prajakwong[2], Steven R Meshnick[3], G Dennis Shanks[1] and Krongthong Thimasarn[4]

[1]US Army Medical Component, Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok; [2]Office of Vector Borne Diseases, Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand; [3]University of North Carolina School of Public Health, Chapel Hill, NC, USA; [4]Roll Back Malaria-Mekong, Bangkok, Thailand

Abstract. Due to the deteriorating efficacy of sulfadoxine-pyrimethamine (SP or Fansidar®), from the mid-1970s the Thai Malaria Control Program was actively involved in testing potential replacement drugs to be used as the primary therapy for falciparum malaria in Thailand. In 1983, a large-scale field trial of mefloquine, a long-acting antimalarial drug known for its efficacy against chloroquine- and SP-resistant *Plasmodium falciparum*, was initiated on the Thai-Cambodian border. The study enrolled over 60,000 patients and eventually led to the formal establishment of mefloquine as the first line drug for the treatment of uncomplicated falciparum malaria in the country. Mefloquine has played a significant role in the control of malaria in Thailand for the past two decades, initially in combination with SP, then by itself, and currently in selected areas as a partner drug in the combination therapy with artesunate. Thailand is the country with the most experience in the use of this drug in a malaria control program. We present here a review of mefloquine's pharmacology and usage in Thailand.

INTRODUCTION

With few exceptions, drug resistant malaria is an increasing problem in all areas of the world where malaria is endemic. The threat of drug resistant malaria continues to be enormous in Africa with a huge health and economic burden posed by malaria. Safe, effective alternatives to chloroquine and sulfadoxine-pyrimethamine (SP) that are affordable by most African malaria control programs have not yet been readily available. In Thailand, antimalarial resistance of *P. falciparum* has progressed to a very advanced stage with multi-drug resistant (MDR) malaria prevalent in most of the endemic areas along the country's international borders. Mefloquine has been a key antimalarial for the treatment of uncomplicated falciparum malaria in Thailand for the last 20 years following the loss of SP efficacy in the country. The pharmacological characteristics of mefloquine and its role in the Thai Malaria Control Program are examined in this review. We aim to provide information that may be useful for other national malaria control programs having to deal with the emergence of MDR malaria.

HISTORY OF MEFLOQUINE

Mefloquine was one of the two licensed drugs developed during a 40-year effort of the US Army Antimalarial Drug Development Program (Shanks, 1994). The Program was set up in the early 1960s for which over 200,000 compounds were screened for antimalarial activity. Mefloquine was first synthesized in 1969 primarily for the purpose of chemoprophylaxis in the military following the then recently discovered threat of chloroquine resistant falciparum malaria.

However, mefloquine usage has not been limited to prophylaxis. Mefloquine was first tested for therapeutic efficacy on a small scale in Thailand in 1976 (Doberstyn *et al*, 1979). During 1983-1985, a large-scale field trial of mefloquine in combination with sulfadoxine and pyrimethamine (Fansimef®, Roche) was conducted. This trial led to the combination being established as standard therapy for Thailand in 1985 (Pinichpongse *et al*, 1987). Resistance to mefloquine was first documented in a non-immune Thai marine recruit as

Correspondence: Chansuda Wongsrichanalai, 130 Sub Street, Bangkok, 10500 Thailand.
E-mail: chansuda@bangkok.th.com

early as 1982 (Boudreau *et al*, 1982). The drug was licensed by the United States Food and Drug Administration (US FDA) in 1989, by which time resistance had already become widespread on the Thai-Cambodian border (Ketrangsee *et al*, 1992; Fontanet *et al*, 1993; Thimasarn *et al*, 1995).

PHARMACOLOGY

Chemical classification

Mefloquine is a quinoline methanol that is chemically closely related with quinine and halofantrine. Its exact mechanism of action is unknown. Interference with the heme detoxification process similar to other quinoline-containing drugs in the blood schizonticidal group has been postulated (Olliaro, 2001).

Disposition

Mefloquine is metabolized in the liver and excreted mainly in feces, but also to some extent in urine, and breast milk. Its elimination half life is 2-6 weeks or 3 weeks on average.

Drug targets and efficacy

Mefloquine is a blood schizonticidal drug that is active against *P. falciparum*, *P. vivax* as well as *P. malariae*. Its target of action is the growing trophozoite stage of the malaria parasite. It is not active against gametocytes or the exoerythrocytic-stage parasites (Olliaro, 2001). When first developed it was highly effective against chloroquine-resistant and SP-resistant strains of *P. falciparum.*

Formulations, indications and dosages

Mefloquine is available for oral administration only because parenteral preparations cause severe local reactions. It is indicated for the treatment of chloroquine-resistant and SP-resistant *P. falciparum*. Originally, mefloquine was recommended at 15 mg/kg single dose. As *P. falciparum* resistant to mefloquine becomes increasingly common in some areas, an increased dose of 25 mg/kg has been recommended to improve its efficacy and possibly delay the progression of resistance. It is usually given in split dose, 6-24 hours apart, because intolerance to high dosage is frequently experienced. Normally, tablets contain 274 mg of mefloquine hydrochloride, which is equivalent to 250 mg of mefloquine base (except in the USA,

where it is available in tablets containing 250 mg of mefloquine hydrochloride or 228 mg mefloquine base (http://www.rocheusa.com/products/lariam/pi.pdf). There are three commercially available preparations and they vary in their bioequivalences (Na-Bangchang *et al*, 2000). Drug bioavailability is improved if taken after meal and by drinking a lot of water.

Mefloquine is an advantageous chemoprophylactic drug, the primary goal of its development. Because of its long elimination half-life, only 250 mg (1 tablet) is required per week. A loading dose regimen is 250 mg daily for 3 consecutive days, preferably starting 2-3 weeks prior to malaria exposure. However, without the initial loading dose, steady state concentrations are not reached for several weeks.

Safety and tolerability

Common, dose-related, adverse effects are dizziness and gastrointestinal disturbances especially nausea and vomiting. Vomiting is relatively frequent in children taking high dose mefloquine. Splitting the dosage 6-24 hours apart helps to reduce vomiting.

Mefloquine is believed to be safe for treatment during the 2nd and 3rd trimesters of pregnancy. Limited data suggested a lack of teratogenic effect and that possibly, it is also safe during the 1st trimester (Smoak *et al*, 1997; McGready and Nosten, 1999; Nosten *et al*, 1999).

Use of mefloquine prophylaxis during pregnancy is somewhat controversial. Mefloquine may also be considered for prophylaxis in women who are pregnant or likely to become so while at risk of exposure to chloroquine-resistant *P. falciparum* (CDC, 2001). However, according to the WHO, pregnancy should be avoided during (and 3 months after completion of) chemoprophylaxis with mefloquine, although pregnancy that occurs while receiving mefloquine prophylaxis is not an indication for induced abortion (WHO, 2001).

Mefloquine is generally well tolerated and can be used by young children (5-15 kilograms or >3 months' old) for both prophylactic and therapeutic purposes (WHO, 2001).

Neuropsychiatric adverse effects

The issue of neuropsychiatric adverse effects

of mefloquine prophylaxis has received a great deal of attention in the popular press in Western countries as well as in medical literature and is subject to diverse opinions. A systematic review of the literature was done in 1997 (Croft and Garner, 1997). In 4 placebo-controlled trials, participants taking prophylactic mefloquine were more likely to withdraw from the study than participants taking placebo (OR = 4.49, 95% CI 1.42-8.56). In 6 trials comparing mefloquine with another antimalarial, participants receiving mefloquine prophylaxis also withdrew more frequently, but this difference was not statistically significant (OR = 1.33, 95% CI, 0.75-2.36). Mefloquine was more likely to cause insomnia and fatigue than alternative drugs.

More recently, a randomized, double-blind, placebo-controlled trial was carried out comparing prophylaxis with mefloquine versus atovaquone-proguanil (Malarone™) in 976 patients (Overbosch et al, 2001). Neuropsychiatric adverse events included insomnia, anxiety, strange or vivid dreams, dizziness or vertigo, depression, visual difficulties and concentration impairment. Overall, these events were more common in the mefloquine group than in the control group (29% vs 14%, p=0.001). Adverse neuropsychiatric events that led to discontinuation of prophylaxis occurred in 5% of the group receiving mefloquine vs 1.2% of the group receiving Malarone™. This study suggests that the neuropsychiatric adverse effects of mefloquine are real.

Neuropsychiatric adverse events have also been reported after mefloquine therapy (Weinke et al, 1991; Hennequin et al, 1994; Ronn et al, 1998). The overall risks vary with ethnic groups with higher percentages being reported in Caucasians and Africans than in Asians (WHO, 2001). However, these three ethnic groups are also different in their health, cultural and geographical backgrounds so it is not possible to know the actual reasons for the differential adverse effects. A search through the computerized database of the Thai Food and Drug Administration for 1998-2001 did not show any reports of neuropsychiatric adverse events in spite of extensive use of mefloquine for malaria treatment in the country (Adverse Product Reaction Monitoring Center, Office of Food and Drug Administration, Ministry of Public Health, Thailand, 2002).

Contraindications

Due to concern over the safety of mefloquine prophylaxis in the Western countries, revised package insert (July 2002) carries the following information: "Use of Lariam® (mefloquine, Roche) is contraindicated in patients with a known hypersensitivity to mefloquine or related compounds (eg quinine and quinidine). Lariam® should not be prescribed for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, or other major psychiatric disorders, or with a history of convulsions" (http://www.lariam.com).

Other contraindications are concurrent use of quinoline-containing drugs such as chloroquine, quinine, halofantrine or a prior treatment with mefloquine within the past four weeks. Because dizziness is a common side effect, people whose activities require fine co-ordination and spatial discrimination such as air-pilots or machinery operators should not take mefloquine.

Drug resistance

Patients maintain sub-therapeutic levels of mefloquine for an extended period following treatment because of its long half-life, thus promoting parasite resistance selection especially in areas where persons are likely to be re-infected with malaria (Wongsrichanalai et al, 2001). P. falciparum resistance to mefloquine usually demonstrates cross-resistance to halofantrine and reduced sensitivity to quinine. Inverse relationship between mefloquine and chloroquine resistance has been observed (Rieckmann, 1990; Winkler et al, 1994). Mefloquine resistance developed soon after its deployment on the Thai-Cambodian border in the mid-1980s and is now widespread in the Mekong region. High levels of resistance are presently common along the Thai-Myanmar and Thai-Cambodian borders. There were also reports of resistance from elsewhere including Papua (in Indonesia, formerly 'Irian Jaya'), Africa, and Brazil (Hoffman et al, 1985; Brasseur et al, 1992, Calvosa et al, 2001). Nonetheless, mefloquine resistance could have been under-reported because recrudescence occurring 28 days after therapy is common and, unless an extended follow-up such as for 42 days applies, late recrudescence is likely to be missed.

USE OF MEFLOQUINE IN THAILAND

Mefloquine-Sulfadoxine-Pyrimethamine (MSP)

Mefloquine was officially adopted as the first line drug for microscopically-confirmed cases of uncomplicated falciparum malaria at all malaria clinics in Thailand in 1985 immediately following the success of an operational trial involving over 60,000 cases of falciparum malaria (Pinichpongse *et al*, 1987). Mefloquine was first available to the Thai Malaria Control Program in the form of MSP (Fansimef®), a fixed dose combination of mefloquine (250 mg), sulfadoxine (500 mg) and pyrimethamine (25 mg). It was given as a single dose of three tablets, thus 750 mg of mefloquine or an equivalent of 15 mg/kg.

Mefloquine monotherapy

Since there was no evidence that SP was beneficial in delaying mefloquine resistance selection and there had been some untoward reactions due to the inadvertent additive effects of antifolates among those receiving prior presumptive SP treatment, a switch to mefloquine monotherapy without SP began in 1990 and by 1996, MSP was completely removed from the Thai Malaria Control Program.

Mefloquine efficacy against uncomplicated *P. falciparum* infections in Thailand was excellent initially. All studies done before 1985, using either mefloquine alone or MSP, had shown efficacy of approaching 100% (Doberstyn *et al*, 1979; Harinasuta *et al*, 1983; Pinichpongse *et al*, 1987).

Artesunate-mefloquine combination

Field efficacy of mefloquine markedly dropped within 5 years of deployment to under 60% on the eastern Thai-Cambodian border (Ketrangsee *et al*, 1992; Fontanet *et al*, 1993; Thimasarn *et al*, 1995) and to 70% on the western Thai-Myanmar border by 1990 (Nosten *et al*, 1991) (Fig 1).

During 1990-1995, quinine-tetracycline was introduced as an interim measure in order to increase malaria cure rates in several areas but this regimen had poor compliance in the outpatient population. Starting in 1995, the Thai Ministry of Public Health decided to replace mefloquine, MSP, or quinine-tetracycline with artesunate co-
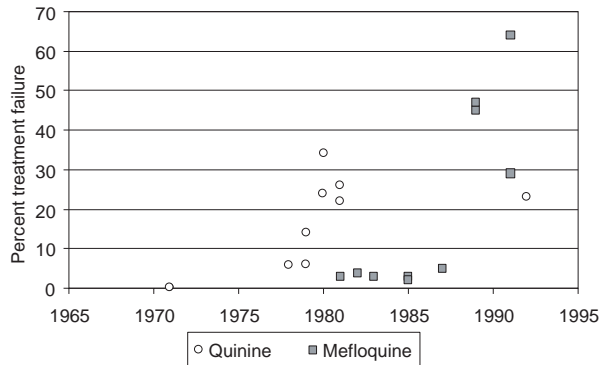

Fig 1–Trends of clinical resistance to mefloquine and quinine in Thailand based on published reports of therapeutic failure.

Mefloquine data (solid squares) from: Harinasuta *et al* (1983); Chongsuphajaisiddhi *et al* (1987); Nosten *et al* (1991); Thimasarn *et al* (1995) (primary and secondary references).

Quinine data (open circles) from: Colwell *et al* (1972); Bunnag and Harinasuta 1987; Chongsuphajaisiddhi *et al* (1981, 1983); Reacher *et al* (1981); Duriyananda and Noeypatimanond (1982a,b); McGready *et al* (1998).

administered with increased dosage of mefloquine (25 mg/kg) in selected areas on the two borders. Those areas had been designated high-level mefloquine resistant.

Artemisinin compounds are known for their rapid action and potent blood schizonticidal effect (Winstanley, 2001). Artesunate is the most widely used artemisinin derivative. It has a half-life of about 45 minutes when given intravenously and about 2 hours orally. There are no common serious side effects. Like other artemisinin derivatives, it should not be given alone because it is often associated with parasite recrudescence after the drug has been cleared without curing the infection. When used in combination with mefloquine, the general recommendation is to give artesunate 200 mg per day for 3 days plus high-dose mefloquine (1,250 mg total) in split dose 6-24 hours apart (WHO, 2001). Dosages are the same for artemether-mefloquine combination, another common artemisinin-based combination therapy (ACT).

According to a review of over 2,000 patients receiving artesunate-mefloquine combination in

more than 10 studies (McIntosh and Olliaro, 2000), parasite clearance, either at Day 7 or Day 28 and later, was better with the combination than with mefloquine monotherapy. Parasite clearance time and fever clearance time were faster with artesunate-mefloquine combination with a weighted mean difference of 20 hours for the former and 10 hours for the latter. A few neuropsychiatric adverse effects were reported in both groups. Vomiting was less frequent in the artesunate-mefloquine group. When compared with artesunate alone, parasite clearance at Day 7 and parasite clearance time and fever clearance time were not significantly better but parasite clearance was more sustainable with artesunate-mefloquine combination. Nausea was more frequent with the combination than with artesunate alone.

An efficacy study conducted on the Thai-Myanmar border using 3-day regimen and another study on the Thai-Cambodian border using 2-day regimen of artesunate-mefloquine combination both demonstrated excellent outcomes. For 4-week follow-up, cure rates were approaching 100%, for 9-week follow-up, cure rates were slightly under 90% (Price *et al*, 1995; Thimasarn *et al*, 1997).

Table 1 shows standard therapies for microscopically-confirmed uncomplicated cases of falciparum malaria at malaria clinics in Thailand as of March 2003. Endemic areas are also classified according to the level of mefloquine resistance as depicted in Fig 2.

Artesunate-mefloquine combination was adopted by the Thai Malaria Control Program because studies in Thailand showed excellent efficacy of this combination and there were no practical alternative choices readily available. Also the 2-day instead of 3-day course was initially selected because of limited data on this combination at that time (1994-1995) and the improved compliance gained with a shorter regimen.

Advantages and disadvantages of artesunate-mefloquine combination

In addition to the known pharmacological advantages of ACT (White, 1999), artesunate-mefloquine combination is also the most studied and used. It is the regimen that the Thai Malaria Control Program has the most confidence for in relation to both efficacy and safety. No significant pharmacological interaction between these two drugs has been found (Giao and de Vries,

Table 1
Antimalarial regimens currently used in the Thai Malaria control Program.

In areas designated as HIGH-LEVEL mefloquine resistant (since 1995)[a].

1st line regimen:

Day 1	ARTESUNATE 300 mg (6 tablets of 50 mg) and MEFLOQUINE 750 mg (3 tablets of 250 mg), followed by 2 tablets (500 mg) at least 6 hours later[b]
Day 2	ARTESUNATE 300 mg and Primaquine 30 mg single dose

2nd line regimen:

Day 1-7	Quinine 600 mg tid and tetracycline 500 mg bid for 7 days

In areas designated as MODERATE-LEVEL mefloquine resistant[b]

1st line regimen:

Day 1	ARTESUNATE 300 mg (6 tablets of 50 mg) and MEFLOQUINE 750 mg (3 tablets of 250 mg)
Day 2	ARTESUNATE 300 mg and Primaquine 30 mg single dose

2nd line regimen:

Day 1-7	Quinine 600 mg tid and tetracycline 500 mg bid for 7 days

In other endemic areas (since 1985)

1st line regimen:

Day 1	MEFLOQUINE 750 mg single dose and Primaquine 30 mg single dose

2nd line regimen:

Day 1-7	Quinine 600 mg tid and tetracycline 500 mg bid for 7 days

For pregnant women:

1st line regimen:

Day 1-7	Quinine 600 mg tid for 7 days

[a]Thai-Myanmar border: Tak Province; Thai-Cambodian border: Trat and Chanthaburi Provinces.
[b]Thai-Myanmar border: Sangkhla Buri district, Thong Pha Phum district and Si Sawat district of Kanchanaburi Povince (since 2002); Thai-Cambodian border: Sa Kaeo Province and Nakhon Nayok Province (since 1999) (See Fig 2).
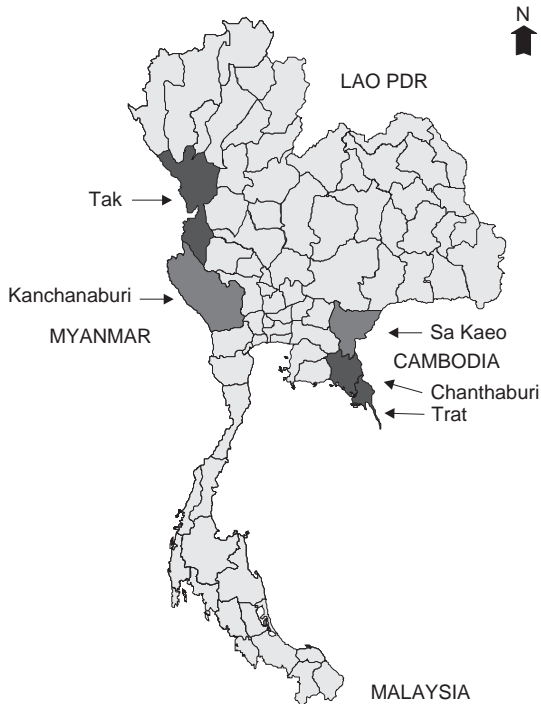
N

Fig 2–Malaria endemic areas in Thailand classified according to their degrees of mefloquine resistance: high-level mefloquine resistant area: provinces of Tak, Trat and Chanthaburi (black) and moderate-level mefloquine resistant area: provinces of Sa Kaeo and Kanchanaburi (gray). Source: malaria statistics, Ministry of Public Health, Thailand, 2001.

2001). By giving artesunate first, the chance of vomiting is reduced thus enhancing mefloquine absorption.

Disadvantages of ACT include high price and multiple dosages resulting in sub-optimal compliance (compared to mefloquine alone). Patients may not take the two drugs together as prescribed and, unlike mefloquine monotherapy, a 2- or 3-day regimen is less convenient. All ACTs are relatively expensive considering the economic status of most endemic countries where malaria is still a major public health burden. Five tablets of mefloquine (1,250 mg) cost around US$1.50-2.00 and 12 tablets of artesunate (600 mg) around US$1.00-1.50 so the price for one treatment of artesunate-mefloquine is approximately US$2.50-3.00 (Ministry of Public Health, Thailand). However, cost is not a problem for Thailand, because

there are under 50,000 cases of falciparum malaria/year requiring this therapy (foreign migrants included). For many other endemic countries, it is an obstacle to malaria control. Lastly, this ACT is among the latest to have emerged from the antimalarial pipeline. If serious ACT treatment failures develop, no obviously superior alternatives to artesunate-mefloquine are as yet available.

Current efficacy, current policy

Combination of artesunate-mefloquine still works well in the areas where it is the first line regimen. Recent *in vivo* studies showed efficacy of over 90% on both Thai-Myanmar and Thai-Cambodian borders (and *in vitro* data have so far indicated no significant worsening of mefloquine resistance over the years (malaria statistics, Ministry of Public Health, Thailand, 2002). However, other efforts to control malaria, such as early diagnosis, case surveillance and vector control are also being sustained by the Thai Malaria Control Program.

In most areas where mefloquine monotherapy has been used since 1985, overall efficacy remains above 80% (malaria statistics, Ministry of Public Health, Thailand, 2002) and the number of falciparum malaria cases continues to decline (Fig 3). This is why the policy to maintain mefloquine monotherapy in such areas still holds. Policy change requires a delicate strategic handling and involves more than a mere acquisition of new drugs and a new policy plan. At the same time there is a growing concern that progressive loss of mefloquine efficacy in the Thai-Myanmar border areas north of Tak Province (see Fig 2), where the drug is still used alone, may necessitate an expanded use of ACT in Thailand. Therefore, debates continue as to whether an adoption of ACT countrywide today would help to prolong the useful lifespan of mefloquine and benefit malaria control in Thailand.

In retrospect

Knowing what we now do about MDR malaria, it seemed that although the MSP was a good idea, SP might not have been appropriate partner drug choice. The drug's usefulness had already been overcome by SP resistance by the time it was deployed in the mid-1980s. Using the higher 25 mg/kg dosage of mefloquine from the beginning would have caused more adverse events, but also

would have cured more patients and might have resulted in a slower emergence of mefloquine resistance. Unfortunately, early trials with 1,000 mg mefloquine per treatment resulted in poor compliance because of intolerable gastrointestinal disturbances. Consequently the idea of increasing the dose of mefloquine monotherapy was prematurely abandoned (J Sirichaisinthop, unpublished data).

THE FUTURE

Use of artesunate in combination with mefloquine in parts of Thailand is in line with the WHO's recommendation that artemisinin compounds should always be used with a partner drug. Artesunate-mefloquine combination has also been adopted as the treatment of choice for falciparum malaria in Cambodia, Vietnam, Brazil, Peru (Peruvian-Brazilian border) and Myanmar. The use of mefloquine monotherapy in Thailand is probably the first and last instance of this regimen in malaria control.

A fixed dose combination of artemether-lumefantrine (Coartem®) has recently been made available at a no-profit price (Winstanley, 2001) or about US$2.50-3.00, which is similar to the current market price in Thailand for one treatment of artesunate-mefloquine. The shorter half-life of lumefantrine (4-6 days) is thought to be an advantage since it may delay drug resistance selection. However, lumefantrine is structurally related to halofantrine and therefore cross-resistance with mefloquine could be expected. Limited clinical trials in Africa and Thailand showed this combination to be safe with 28-day cure rates of over 95% reported. However, a 6-dose (3-day) regimen, as opposed to a 4-dose (2-day), was necessary to achieve such excellent cure rates especially in areas with MDR malaria (van Vugt *et al*, 1998; Looareesuwan *et al*, 1999; Lefevre *et al*, 2001). More clinical data are required and more information is needed about how this combination could be used in a malaria control program rather than individual patient treatments.

The use of mefloquine for malaria prophylaxis continues in some traveler populations, but it is increasingly being replaced by atovaquone-proguanil combination (Malarone™) especially in persons who are concerned about the poorly
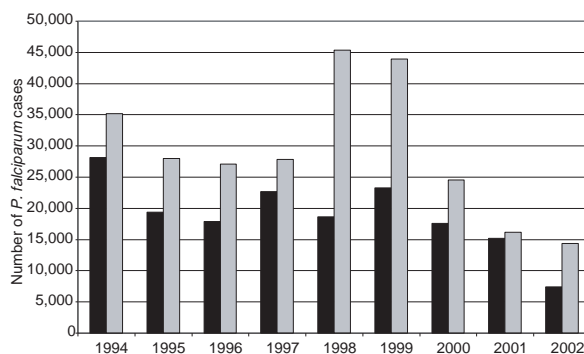

Fig 3–Annual number of falciparum malaria cases among Thai people (foreign migrants not included) from 1994 to 2002 in provinces where mefloquine-artesunate combination has been used since 1995 (black) and where mefloquine alone remained the first line drug in 2002 (gray). The marked increase in the number of cases in the latter during 1998-1999 was the result of malaria epidemic in mefloquine-sensitive areas of southern Thailand and budgetary cut following the Asian economic crisis in 1997; given the limited funds, malaria control emphasis was placed on areas where drug resistance was more intense (black).
Source: Malaria statistic, Ministry of Public Health, Thailand, 2002.

understood neuropsychiatric adverse events attributed to mefloquine. The Thai Malaria Control Program does not generally recommend any chemoprophylaxis, but encourages personal protection against mosquito bites, because no known regimen is reliably effective against parasites in this region.

Conclusions

The outcome of mefloquine use in the control of malaria in Thailand can be viewed from two perspectives. In provinces where mefloquine monotherapy continues to be effective, mefloquine has contributed to an overall reduction of falciparum malaria cases (Fig 3).

In parts of endemic areas along the Thai-Myanmar and Thai-Cambodian borders, mefloquine resistance has necessitated the introduction of artesunate-mefloquine combination therapy. The loss of mefloquine efficacy in such areas during the late 1980s and early 1990s exemplifies the danger of introducing a long-acting anti-

malarial chemotherapy in high transmission areas, where implementation of other control strategies is blocked. It is unlikely that mefloquine alone will ever re-gain its clinical efficacy in such areas. Since any expected alternatives to ACT are even more difficult for operational use, expensive and possibly more toxic, it is important that other countries introducing ACT do it effectively in order to delay the selection of drug resistant falciparum malaria.

ACKNOWLEDGEMENTS

REFERENCES

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

Brasseur P, Kouamouo J, Moyou RS, Druilhe P. Mefloquine resistant malaria in Cameroon and correlation with resistance to quinine. *Mem Inst Oswaldo Cruz* 1992; 87 (suppl 3): 271-3.

Bunnag D, Harinasuta T. Quinine and quinidine in malaria in Thailand. *Acta Leiden* 1987; 55: 163-6.

Calvosa VS, Adagu IS, Povoa MM. *Plasmodium falciparum*: emerging mefloquine resistance in vitro in Para state, north Brazil. *Trans R Soc Trop Med Hyg* 2001; 95: 330-1.

CDC. Health information for international travel, 2001-2002. Atlanta, GA: Centers for Diseases Control and Prevention, 2001.

Chongsuphajaisiddhi T, Sabcharoen A, Attanath P. *In vivo* and *in vitro* sensitivity of falciparum malaria to quinine in Thai children. *Ann Trop Paediatr* 1981; 1: 21-6.

Chongsuphajaisiddhi T, Sabchareon A, Attanath P. Treatment of quinine resistant falciparum malaria in Thai children. *Southeast Asian J Trop Med Public Health* 1983; 14: 357-62.

Chongsuphajaisiddhi T, Sabchareon A, Chantavanich P, *et al*. A phase-III clinical trial of mefloquine in children with chloroquine-resistant falciparum malaria in Thailand. *Bull WHO* 1987; 65: 223-6.

Colwell EJ, Neopatimanondh S, Sadudee N. Investigations of the quinine sensitivity of *Plasmodium falciparum* in central Thailand. *Southeast Asian J Trop Med Public Health* 1972; 3: 496-500.

Croft A, Garner P. Mefloquine to prevent malaria: a systematic review of trials. *Br Med J* 1997; 315: 1412-6.

Doberstyn EB, Phintuyothin P, Noeypatimanondh S, Teerakiartkamjorn C. Single-dose therapy of falciparum malaria with mefloquine or pyrimethamine-sulfadoxine. *Bull WHO* 1979; 57: 275-9.

Duriyananda D, Noeypatimanond S. Quinine sensitivity of *Plasmodium falciparum* in Phra Phutthabat Hospital. A retrospective study. *J Med Assoc Thai* 1982a; 65: 599-602.

Duriyananda D, Noeypatimanond S. Quinine-resistant falciparum malaria: case report. *J Med Assoc Thai* 1982b; 65: 395-8.

Fontanet AL, Johnston DB, Walker AM, *et al*. High prevalence of mefloquine-resistant falciparum malaria in eastern Thailand. *Bull WHO* 1993; 71: 377-83.

Giao PT, de Vries PJ. Pharmacokinetic interactions of antimalarial agents. *Clin Pharmacokinet* 2001; 40: 343-73.

Harinasuta T, Bunnag D, Wernsdorfer WH. A phase II clinical trial of mefloquine in patients with chloroquine-resistant falciparum malaria in Thailand. *Bull WHO* 1983; 61: 299-305.

Hennequin C, Bouree P, Bazin N, Bisaro F, Feline A. Severe psychiatric side effects observed during prophylaxis and treatment with mefloquine. *Arch Intern Med* 1994; 154: 2360-2.

Hoffman SL, Rustama D, Dimpudus AJ, *et al*. RII and RIII type resistance of *Plasmodium falciparum* to combination of mefloquine and sulfadoxine/pyrimethamine in Indonesia. *Lancet* 1985; 2: 1039-40.

Ketrangsee S, Vijaykadga 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.

Lefevre G, Looareesuwan S, Treeprasertsuk S, *et al*. A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant *Plasmodium falciparum* malaria in Thailand. *Am J Trop Med Hyg* 2001; 64: 247-56.

Looareesuwan S, Wilairatana P, Chokejindachai W, *et al*. A randomized, double-blind, comparative trial of a new oral combination of artemether and benflumetol (CGP 56697) with mefloquine in the treatment of acute *Plasmodium falciparum* malaria

in Thailand. *Am J Trop Med Hyg* 1999; 60: 238-43.

McGready R, Cho T, Hkirijaroen L, *et al*. Quinine and mefloquine in the treatment of multidrug-resistant *Plasmodium falciparum* malaria in pregnancy. *Ann Trop Med Parasitol* 1998; 92: 643-53.

McGready R, Nosten F. The Thai-Burmese border: drug studies of *Plasmodium falciparum* in pregnancy. *Ann Trop Med Parasitol* 1999; 93 (suppl 1): S19-23.

McIntosh HM, Olliaro P. Artemisinin derivatives for treating uncomplicated malaria. *Cochrane Database Syst Rev* 2000; CD000256.

Na-Bangchang K, Karbwang J, Palacios PA, Ubalee R, Saengtertsilapachai S, Wernsdorfer WH. Pharmacokinetics and bioequivalence evaluation of three commercial tablet formulations of mefloquine when given in combination with dihydroartemisinin in patients with acute uncomplicated falciparum malaria. *Eur J Clin Pharmacol* 2000; 55: 743-8.

Nosten F, ter Kuile F, Chongsuphajaisiddhi T, *et al*. Mefloquine-resistant falciparum malaria on the Thai-Burmese border. *Lancet* 1991; 337: 1140-3.

Nosten F, Vincenti M, Simpson J, *et al*. The effects of mefloquine treatment in pregnancy. *Clin Infect Dis* 1999; 28: 808-15.

Olliaro P. Mode of action and mechanism of resistance for antimalarial drugs. *Pharmacol Ther* 2001; 89: 207-19.

Overbosch D, Schilthuis H, Bienzle U, *et al*. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. *Clin Infect Dis* 2001; 33: 1015-21.

Pinichpongse S, Suebsaeng L, Malikul S, Doberstyn EB, Rooney W. The operational introduction of mefloquine, a new antimalarial drug, by the malaria programme of Thailand. *Commun Dis J Thai* 1987; 13: 411-24.

Price RN, Nosten F, Luxemburger C, *et al*. Artesunate versus artemether in combination with mefloquine for the treatment of multidrug-resistant falciparum malaria. *Trans R Soc Trop Med Hyg* 1995; 89: 523-7.

Reacher M, Campbell CC, Freeman J, Doberstyn EB, Brandling-Bennett AD. Drug therapy for *Plasmodium falciparum* malaria resistant to pyrimethamine-sulfadoxine (Fansidar). A study of alternate regimens in eastern Thailand, 1980. *Lancet* 1981; 2: 1066-9.

Rieckmann KH. Monitoring the response of malaria infections to treatment. *Bull WHO* 1990; 68: 759-60.

Ronn AM, Ronne-Rasmussen J, Gotzsche PC, Bygbjerg IC. Neuropsychiatric manifestations after mefloquine therapy for *Plasmodium falciparum* malaria: comparing a retrospective and a prospective study. *Trop Med Int Health* 1998; 3: 83-8.

Shanks GD. The rise and fall of mefloquine as an antimalarial drug in South East Asia. *Mil Med* 1994; 159: 275-81.

Smoak BL, Writer JV, Keep LW, Cowan J, Chantelois JL. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. *J Infect Dis* 1997; 176: 831-3.

Thimasarn K, Sirichaisinthop J, Chanyakhun P, Palananth C, Rooney W. 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.

Thimasarn K, Sirichaisinthop J, Vijaykadga 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.

Van Vugt M, Brockman A, Gemperli B, *et al*. Randomized comparison of artemether-benflumetol and artesunate-mefloquine in treatment of multidrug-resistant falciparum malaria. *Antimicrob Agents Chemother* 1998; 42: 135-9.

Weinke T, Trautmann M, Held T, *et al*. Neuropsychiatric side effects after the use of mefloquine. *Am J Trop Med Hyg* 1991; 45: 86-91.

White N. Antimalarial drug resistance and combination chemotherapy. *Philos Trans R Soc Lond B Biol Sci* 1999; 354: 739-49.

World Health Organization. The use of antimalarial drugs. Report of an informal consultation, Geneva, Switzerland, 13-17 November 2001. *WHO/CDS/RBM/2001,* 2001: 33.

Winkler S, Brandts C, Wernsdorfer WH, Graninger W, Bienzle U, Kremsner PG. Drug sensitivity of *Plasmodium falciparum* in Gabon. Activity correlations between various antimalarials. *Trop Med Parasitol* 1994; 45: 214-8.

Winstanley P. Modern chemotherapeutic options for malaria. *Lancet Infect Dis* 2001; 1: 242-50.

Wongsrichanalai C, Sirichaisinthop J, Karwacki JJ, *et al*. Drug resistant malaria on the Thai-Myanmar and Thai-Cambodian borders. *Southeast Asian J Trop Med Public Health* 2001; 32: 41-9.