MEFLOQUINE – ITS 20 YEARS IN THE THAI MALARIA CONTROL PROGRAM

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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...
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 *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 \textit{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-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).

**Table 1**

<table>
<thead>
<tr>
<th>Antimalarial regimens currently used in the Thai Malaria control Program.</th>
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<tbody>
<tr>
<td><strong>In areas designated as HIGH-LEVEL mefloquine resistant (since 1995)</strong>^a^</td>
</tr>
<tr>
<td>1st line regimen: Day 1</td>
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<tr>
<td>2nd line regimen: Day 1-7</td>
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<tr>
<td><strong>In areas designated as MODERATE-LEVEL mefloquine resistant</strong>^b^</td>
</tr>
<tr>
<td>1st line regimen: Day 1</td>
</tr>
<tr>
<td>2nd line regimen: Day 1-7</td>
</tr>
<tr>
<td><strong>In other endemic areas (since 1985)</strong></td>
</tr>
<tr>
<td>1st line regimen: Day 1</td>
</tr>
<tr>
<td>2nd line regimen: Day 1-7</td>
</tr>
<tr>
<td><strong>For pregnant women:</strong></td>
</tr>
<tr>
<td>1st line regimen: Day 1-7</td>
</tr>
</tbody>
</table>

^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 Province (since 2002); Thai-Cambodian border: Sai Kaeo Province and Nakhon Nayok Province (since 1999) (See Fig 2).
Mefloquine in Thailand

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 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.

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