

MEFLOQUINE CHEMOPROPHYLAXIS OF SOLDIERS ON THE THAI-CAMBODIAN BORDER

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Abstract. Chemoprophylaxis of malaria on the Thai-Cambodian border is difficult due to the high level of drug resistance. Thirteen separate companies of Royal Thai Marine Militia were placed on 250 mg weekly mefloquine chemoprophylaxis from August 1989 to January 1990. A mean number of 722 soldiers received two or more doses of mefloquine per month for the five month study. The medication was well tolerated and compliance averaged 91%. Substantial numbers of prophylaxis breakthroughs were seen which resulted in 3.2 cases of malaria/100 man-months. Sixty-eight falciparum malaria cases were documented in men who had taken at least two mefloquine doses in the previous four weeks. No serious neuropsychiatric reactions occurred. Mefloquine chemoprophylaxis failures exist on the Thai-Cambodian border and are one sign of the spread of mefloquine resistance.

INTRODUCTION

The selection of an adequate chemoprophylactic agent for use on the Thai-Cambodian border is difficult since chloroquine and pyrimethamine/sulfadoxine became ineffective against falciparum malaria. In 1977 field trials in Thailand showed that mefloquine was a very effective chemoprophylactic agent (Pearlman *et al*, 1980). Subsequent trials in Burmese soldiers (Win *et al*, 1985) and Thai migrant workers (Kamolratanakul *et al*, 1989) demonstrated the superiority of mefloquine containing combinations as opposed to sulfadoxine/pyrimethamine alone. Despite the high cost and reports of rare psychotic reactions (Bjorkman, 1989), we elected to use mefloquine chemoprophylaxis in selected Royal Thai Marine Militia units because of the high failure rates seen with the previously standard regimen of weekly pyrimethamine 12.5 mg/ dapson 100 mg. This report details the outcome of this large-scale field use of mefloquine in an area of known intense drug resistance.

The opinions or assertions contained in this paper are private views of the authors and are not to be construed as official or as reflecting the views of the Royal Thai Navy or the United States Army.

MATERIALS AND METHODS

Thirteen companies of Royal Thai Marine Militia on the southeastern Cambodian border with a combined strength of 750 men were chosen for mefloquine chemoprophylaxis based on high malaria attack rates (> 5%/month) during 1988-89. Mefloquine was given as 250 mg (salt) every week of a United States Army preparation manufactured by Hoffman-La Roche. Mefloquine distribution began on 15 August 1989 and ended 30 January 1990. Due to a troop rotation in October 1989, 1307 men actually received mefloquine. New units received two weeks of mefloquine prior to deployment to the border region.

The medication was distributed by unit medics from computer-generated forms which had standardized questions about compliance and side effects. Returned forms had unused medication still attached. Compliance was defined as the number of men noted to have received mefloquine divided by the number of men eligible to receive it in that unit. All men had a thick blood film taken every 10 days to detect any parasitemia. Films were stained with Giemsa and not called negative until 100 oil-immersion fields were examined without finding plasmodia. Men with falciparum parasitemia were eligible for inclusion in a halo-

fantrine study (Shanks *et al*, 1991) or given quinine/tetracycline. Chloroquine/primaquine was used to treat vivax malaria.

A parasitemia was defined as a mefloquine failure if the soldier was known to have taken two of the last four doses of mefloquine. This criterion was used because of the report of chemoprophylactic success with mefloquine 250 mg given every other week (Eamsila, 1989). Soldiers with parasitemia taking less than two of the last four mefloquine doses were regarded as compliance failures.

RESULTS

Fig 1 shows the monthly cases of falciparum and vivax malaria distinguished as mefloquine or compliance failures. A total of 87 falciparum malaria cases were found with 68 mefloquine failures and 19 compliance failures. A total of 44 vivax malaria cases were found with 30 mefloquine failures and 14 compliance failures. The falciparum attack rate overall was 1.9/100 man-months for mefloquine failures and 0.3/100 man-months for compliance failures. The vivax attack rate overall was 0.8/100 man-months for mefloquine failures and 0.2/100 man-months for compliance failures.

Some units had higher malaria attack rates probably due to increased exposure to the jungle. Fig 2 shows the cumulative malaria attack rate by week in three companies from such a unit. The malaria attack rate approximates 1% week.

Over the 22 weeks of mefloquine chemoprophylaxis a total of 17,284 man-weeks of medication were received with an overall compliance rate of 91%. Weekly compliance had a range of 83-95%. The most common reason (57%) a man did not receive his mefloquine was absence from the unit on official leave. Treatment for malaria and absences not due to leave were the other reasons men did not receive their mefloquine and accounted for 43% of the men who were noncompliant.

Side effects attributed by the medic or the soldier to mefloquine were unusual despite the weekly query for nine common problems. Only 1.2% of man-weeks were marked by an identified side effect. No serious problems including central

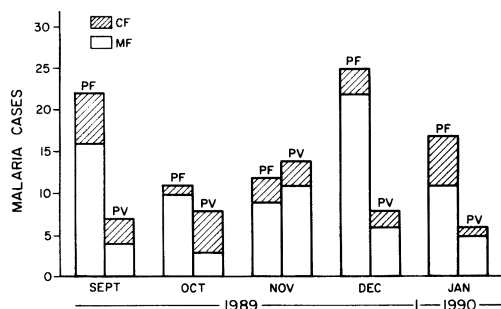


Fig 1—Number of cases of falciparum and vivax malaria by month separated by the soldier's compliance status on mefloquine chemoprophylaxis. MF = mefloquine failure, CF = compliance failure (see text)

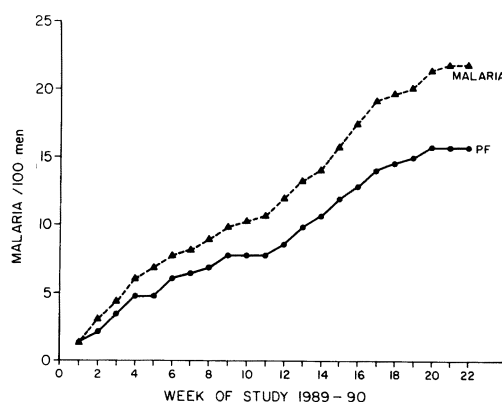


Fig 2—Cumulative malaria attack rate/100 men (falciparum and all malaria) by week from 3 companies of soldiers in the same battalion on the Thai-Cambodian border.

nervous system reactions were seen. The most common problems were due to dizziness, headache or gastrointestinal discomfort which did not cause the man to stop taking mefloquine. Other problems were reported infrequently (Table 1).

DISCUSSION

This report details our experience with mefloquine chemoprophylaxis in an area known for a high level of drug resistance. It was not designed as a comparative trial as there is no control group.

Table 1

Episodes (percentages) of side effects reported by soldiers receiving weekly mefloquine prophylaxis
214/17,284 man-weeks.

dizziness	85 (40)	rash	8 (4)
nausea	33 (15)	vomit	5 (2)
multiple side effects	33 (15)	stomach pain	3 (1)
headache	26 (12)	fever	2 (1)
diarrhea	18 (8)	anorexia	1 (0.5)

Compliance was monitored closely by unit medics but was not universally witnessed. The number of falciparum malaria break-throughs while taking mefloquine indicates mefloquine resistance. Further evidence that these falciparum cases are truly resistant to mefloquine was presented in another report which showed an average of 950 ng/ml mefloquine in the blood upon presentation with parasitemia and a elevated concentration of mefloquine required to inhibit the isolated parasites *in vitro* (Shanks *et al*, 1991). These chemoprophylactic findings support the Thai Malaria Division's report of an increasing number of mefloquine treatment failures in the same region (Report on Borai, 1990, unpublished). These data also confirm the observations from Africa which indicate that mefloquine must truly be taken every week (Lobel *et al*, 1991).

Despite the large amount of mefloquine given over five months, the drug was quite well tolerated. No neuropsychiatric reactions were seen. Rare side effects cannot be ruled out, but neuropsychiatric reactions have not yet been confirmed in Asians receiving prophylactic mefloquine.

This information is not encouraging to physicians and public health authorities who must make chemoprophylactic recommendations for persons living and working on the Thai-Cambodian border. It is important to note that the actual endemic area in Thailand is usually limited to a very narrow area of rain forest on the international border. For persons exposed to this zone especially at night, there simply is no ideal chemoprophylactic option which will reliably prevent all malaria. Mefloquine certainly works better than pyrimethamine/sulfadoxine (Eamsila *et al*, 1989) or pyrimethamine/dapsone (Watanasook *et al*,

1989). Doxycycline has been tested in a controlled field trial in some of the same military units in 1987 (Watanasook *et al*, 1989). The overall malaria rate when using doxycycline 100 mg daily of 19% in 17 weeks is quite similar to that described with mefloquine in this report. Other studies indicate that 200 mg proguanil combined with 1,500 mg sulfamethoxazole daily can provide protection but at a lower efficacy than doxycycline or mefloquine (Karwacki *et al*, 1991).

The Thai-Cambodian border is an area of considerable international interest because of the presence of a large number of Khmer refugees and the continuing guerilla war in Cambodia. Persons who are unavoidably exposed to malaria in this region need to be aware that chemoprophylactic failures occur with mefloquine, the need to use antimosquito measures such as nets and repellents, and the importance of quickly seeking expert medical advice should they experience a febrile illness.

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REFERENCES

- Bjorkman A. Acute psychosis after mefloquine. *Lancet* 1989; 2 : 865.

- Eamsila C, Singharaj P, Yooyen P, *et al.* Prevention of malaria by Fansimef given biweekly. *R Thai Army Med J* 1989; 42 : 149-53.
- Kamolratanakul P, Viputsiri O, Dhanamun B, Hirunabut S, Mekmasin A, Thongsawat P. The effectiveness of chemoprophylaxis against malaria for non-immune migrant workers in Eastern Thailand. *Trans R Soc Trop Med Hyg* 1989; 83 : 313-5.
- Karwacki JJ, Shanks GD, Suriyamongkol V, Watanasook C. Proguanil/sulfamethoxazole malaria chemoprophylaxis on the Thai-Cambodian border. *Southeast Asian J Trop Med Public Health* 1991; 22 : 77-80.
- Lobel HO, Bernard KW, Williams SL, Hightower, AW, Patchen LC, Campbell CC. Effectiveness and tolerance of long-term malaria prophylaxis with mefloquine. *JAMA* 1991; 265 : 361-4.
- Pearlman. EJ, Doberstyn EB, Sudsok S, Thiemanun W, Kennedy RS, Canfield CJ. Chemosuppressive field trials in Thailand. *Am J Trop Med Hyg* 1980; 29 : 1131-7.
- Shanks GD, Watt G, Edstein MD, *et al.* Halofantrine for the treatment of mefloquine chemoprophylaxis failures. *Am J Trop Med Hyg* 1991; 45 : 488-91.
- Watanasook C, Singharaj P, Suriyamongkol V, *et al.* Malaria prophylaxis with doxycycline in soldiers deployed to the Thai-Kampuchean border. *Southeast Asian J Trop Med Public Health* 1989; 20 : 61-4.
- Win K, Thwe Y, Lwin TT, Win K. Combination of mefloquine with sulfadoxine-pyrimethamine compared with two sulfadoxine-pyrimethamine combinations in malaria chemoprophylaxis. *Lancet* 1985; 1 : 694-5.
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