JITMM Proceedings
www.jitmm.com/proceeding
J I T M M Proceedings 7 (2018) 35-44

COMPLIANCE AND REPORTED ADVERSE EFFECTS OF MALARIA CHEMOPROPHYLAXIS AMONG TRAVELERS: A PROSPECTIVE STUDY

Jitfa Loorungroj [1], Watcharapong Piyaphanee [2], Udomsak Silachamroon [2], Sant Muangnoicharoen [2], Natthida Sriboonvorakul [2], Wattana Leowattana [2], Suda Punrin [3], Polrat Wilairatana [2], Pornthep Chanthavanich [4]

[1] Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
[2] Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
[3] Queen Saovabha Memorial Institute, The Thai Red Cross Society, Bangkok, Thailand
[4] Department of Tropical Pediatrics, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

ABSTRACT

Background: The number of international travelers to malaria-endemic areas has increased in recent years. Many studies have been conducted in European countries to determine compliance with antimalarial prophylaxis and adverse effects. However, no previous studies have been conducted among Thai travelers, whose practices may differ from their European counterparts. This study aimed to determine compliance with malaria chemoprophylaxis and find the incidence of mefloquine-, atovaquone-proguanil- and doxycycline-related adverse effects among Thai and foreign travelers.

Methods: Thai and foreign travelers who attended the travel clinic and planned to travel in a malaria-endemic area for < 3 months were enrolled into the study. Follow-up was by post-travel electronic questionnaire or telephone interview within 7 days after they had completed the medication.

Results: This preliminary result consisted of 130 participating travelers (79% Thai and 21% other nationalities); the mean age was 42 years, and the median trip duration 10 days. Africa was the most popular destination. Atovaquone-proguanil was the most commonly prescribed drug, followed by doxycycline and mefloquine.

Overall, compliance was good among 75% of participants; 23% of travelers displayed adverse effects. The most common adverse effect was GI symptoms (16.9%). There was no statistically significant difference in adverse effects reported by those taking atovaquone-proguanil and those taking doxycycline (19% vs 32%, p=0.15). This may be due to the small number of participants.

Conclusion: About a quarter of travelers did not complete the course of chemoprophylaxis. Most travelers could tolerate the adverse effects. To raise awareness of adhering to the drug regimen, pre-travel counseling is essential.

Keywords: Malaria chemoprophylaxis, Compliance, Adverse effects

INTRODUCTION

Malaria is a significant diagnosis for fever among returned travelers. It was the most common specific diagnosis in ill returned travelers seen at the GeoSentinel clinic from 1997 to 2006 (Wilson ME *et al*, 2007). Falciparum malaria also accounted for 33% of deaths among febrile returned travelers who had visited Oceania or the Pacific Islands and sub-Saharan Africa travelers (Wilson ME *et al*, 2007). Chemoprophylaxis might be recommended in some high risk areas to reduce the risk of getting malaria. Without chemoprophylaxis, the risk of malaria in travelers is as high as > 20% per month in Oceania, and 2% per month in sub-Saharan Africa (Ryan ET *et al*, 2000). Many studies have shown that chemoprophylaxis has good efficacy to prevent malaria infection (Bradley DJ *et al*, 1995;

Correspondence: Dr. Jitfa Loorungroj
Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, 420/6 Ratchawithi Road, Ratchathewi, Bangkok 10400, Thailand
Phone : +66(0)23069145
Fax : +66(0)23069145
E-mail : Jitfah@thaitravelclinic.com

Tan KR *et al*, 2011). However, failure to complete a full course of antimalarial prophylaxis results in reduced chemoprophylaxis effectiveness and increased risk of developing malaria (Steffen R *et al*, 1990; Kitchener SJ *et al*, 2005).

Many previous studies of European travelers showed full compliance rates varied from 50-90% (Carme B *et al*, 1997; Chatterjee S *et al*, 1999; Hoebe C *et al*, 1997; Landman KZ *et al*, 2015; Lobel HO *et al*, 2001; Soto J *et al*, 2006; Steffen R *et al*, 1990). However, Asian travelers may have lower levels of awareness of malaria risk and drug compliance than Western travelers (Kimura M *et al*, 2006; Namikawa *et al*, 2008; Yoo Y-J *et al*, 2007; Zhang M *et al*, 2011). The number of Thai travelers to Africa has increased in recent years; nevertheless, the use of malaria prophylaxis among Thai travelers has not been studied before. The use of chemoprophylaxis among Thai travelers may be poor, especially compared with Western travelers.

Mefloquine, doxycycline, and atovaquone-proguanil are recommended drugs for chemoprophylaxis in chloroquine-resistant P. falciparum areas. The adverse effects of these drugs are usually mild and most users tolerate the drugs well (Landman KZ *et al*, 2015; Nasveld PE *et al*, 2010; Overbosch D *et al*, 2001). Severe adverse effects leading to hospitalization are very rare. Neuropsychriatic adverse effects have been associated with mefloquine (Kitchener SJ *et al*, 2005; Lobel HO *et al*, 2001) but serious neuropsychiatric effects are rare, in the range 1/10,000 to 1/13,000 of prophylaxis users (Kitchener SJ *et al*, 2005; Schlagenhauf P *et al*, 1999). The primary objectives were to determine the compliance and incidence of self-reported adverse effects of mefloquine, doxycycline, and atovaquone-proguanil in Thai and foreign travelers who planned to go to malaria-endemic countries for < 3 months and used one of these drugs as chemoprophylaxis. We also aimed to determine factors associated with compliance, compare adverse effects among the 3 drugs, as well as compliance between Thai and foreign travelers as secondary objectives.

MATERIALS AND METHODS

This study was a questionnaire-based prospective cohort study among Thai and foreign travelers who planned to go to malaria-endemic areas for < 3 months and visited the travel clinic, Hospital for Tropical Diseases, Faculty of Tropical Medicine, Mahidol University, for pre-travel counseling. According to the SOP of the travel clinic, all Thai and foreign travelers recommended to take chemoprophylaxis by the doctor, and who met the inclusion criteria, were invited to participate in the study. Inclusion criteria included people aged between 18 and 70 years, planning to travel in a malaria-endemic area for < 3 months, and agreement to take malaria chemoprophylaxis. Pregnant women and those unable to read and write were not enrolled into the study.

The malaria chemoprophylactic drugs used in the travel clinic included mefloquine, doxycycline, and atovaquone-proguanil. The choice of chemoprophylaxis was decided among doctors and travelers after intensive discussions of the three regimens, contraindications, and potential side effects. Atovaquone-proguanil and doxycycline were advised to be taken as 1 tablet per day, beginning 1-2 days before travel to a malaria-endemic area and continued until 7 days and 4 weeks after return, for atovaquone-proguanil and doxycycline, respectively. Mefloquine was advised to be taken as 1 tablet once a week, starting at least 2 weeks before travel and continued until 4 weeks after return. Apart from malaria chemoprophylaxis, all travelers were advised to use mosquito prevention such as repellent, bed net, wearing long-sleeved shirt and pants. The participants who agreed to participate in the study were asked to answer a pre-travel questionnaire by themselves at the first visit. The pre-travel questionnaire included questions regarding personal data, travel plan (such as destination, duration, travel purpose and accommodation), previous prophylaxis use, and previous malaria infection.

Participants were followed up by telephone or e-mail within 1 week after their anticipated date of the last tablet. The post-travel questionnaire

consisted of questions regarding drug compliance, mosquito protective measures, adverse effects, severity and onset of adverse effects. Full compliance was defined as missing < 10% of all tablets, including doses started before and after return from the malarious area. The data-collection period was 1 year (December 2016-December 2017). The calculated sample size was 250 people. Data were analyzed using SPSS software version 18.0. The Chi-square test was used for categorical data and student's *t*-test for continuous data; a *p*-value < 0.05 was regarded as statistically significant. Full compliance was defined as missing < 10% of all tablets and noncompliance was missing 10% or more of all tablets.

RESULTS

At the time of data analysis, 227 travelers were enrolled. Of these, 4 participants were excluded, 76 were awaiting follow-up, and 147 had been followed up. 8 participants were lost to follow-up, and 9 canceled their trips. This preliminary study included 130 participants who were completely followed up and whose data were analyzed.

Of the 130 participants, 103 (79%) were Thai and 27 (21%) foreigners. The demographic characteristics of the participants are shown in Table 1. The ratios of male to female was equal among both Thai and foreign travelers. The overall mean age was 42 years, with the majority in the range 30-45 years. The median trip duration was 10 days. Africa was the most common destination for both groups. Atovaquone-proguanil was the most commonly prescribed drug, followed by doxycycline and mefloquine. Leisure was the most common purpose of travel. Most participants have never used malaria chemoprophylaxis or had a previous malaria infection.

Our study found that 75.4% of all participants complied fully, while 24.6% did not. When Thai and foreign travelers were compared, the percentages for full compliance were not statistically significantly different (73.8% vs 81.5%, *p*-value = 0.4). The results from intention-to-treat analysis, including 8 lost to follow-up participants (138 participants) and all of them were assumed as noncompliant were little different from the per-protocol analysis(130 participants), which yielded 71% full compliance. However, foreign-traveler compliance was lower than Thai compliance (73.8% vs 64.7%, *p*-value=0.3), but without statistically significant difference. Perceived uselessness of the drug was the main reason for noncompliance, accounting for almost half (46.7%), followed by forgetting (25%) to take the drug, while 12.5% of noncompliant participants withdrew from taking the drug either because of fear or actually experiencing adverse effects (Figure 1). Compliance among those taking atovaquone-proguanil was better than doxycycline or mefloquine, with statistical significance, when comparing between

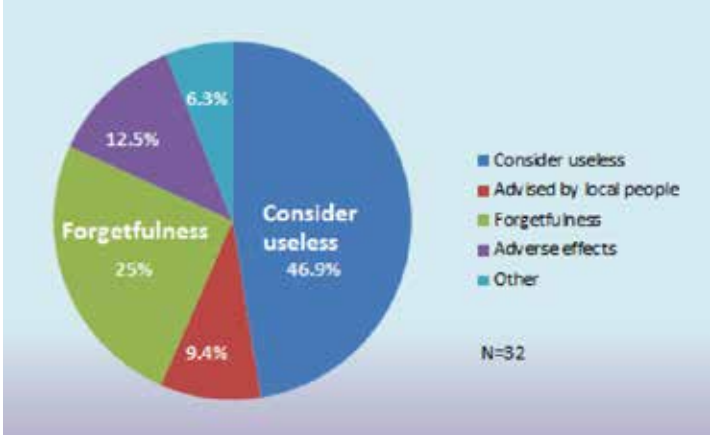

Fig 1- Reasons for noncompliance

Table 1 Demographic characteristics of the participants

Characteristic	Total N=130	Thai N=103	Foreigner N=27
Sex			
Male	67 (51.5%)	50 (48.5%)	17 (63%)
Female	63 (48.5%)	53 (51.5%)	10 (37%)
Age			
<30	26 (20%)	20 (19.4%)	6 (22.2%)
30-45	51 (39.2%)	40 (38.8%)	11 (40.7%)
46-60	39 (30%)	34 (33.0%)	5 (18.5%)
>60	14 (10.8%)	9 (8.7%)	5 (18.5%)
Mean age(years) ± SD	42.38±12.71	42.42±12.17	42.26±14.86
Median duration(IQR)(days)	10 (7-15.25)	10 (7-14)	15 (10-35)
Drug			
atovaquone-proguanil	84 (64.6%)	66 (64.1%)	18 (66.6%)
doxycycline	29 (22.3%)	24 (23.3%)	5 (18.5%)
mefloquine	17 (13.1%)	13 (12.6%)	4 (14.9%)
Destination			
Africa	108 (83.1%)	87 (84.5%)	21 (77.8%)
Asia	3 (2.3%)	2 (1.9%)	1 (3.7%)
Oceania	15 (3.1%)	14 (13.6%)	1 (3.7%)
South America	4 (11.5%)	-	4 (14.8%)
Purpose			
Leisure			
Backpack	57 (42.5%)	40 (37.6%)	17 (60.9%)
Group tour	28 (21.5%)	25 (24.3%)	3 (11.7%)
Work			
Business	10 (7.7%)	9 (8.7%)	1 (3.7%)
Worker	30 (22.6%)	26 (24.6%)	4 (14.8)
VFR	3 (2.3%)	3 (2.3%)	-
Volunteer	5 (3.4%)	2 (7.8%)	3 (8.9%)
Accommodation			
Luxury hotel	77 (44%)	67 (48.3%)	10 (23.2%)
Budget hotel	19 (11%)	10 (7.2%)	9 (21%)
Guest house	21 (12%)	13 (9.3%)	8 (18.6%)
Local home	17 (10%)	11 (7.9%)	6 (14%)
Camp	40 (23%)	38 (27.3%)	10 (23.2%)
Previous malaria prophylaxis			
No	98 (75.4%)	86 (83.5%)	12 (44.4%)
Yes	32 (24.6%)	17 (16.5%)	15 (55.6%)

Characteristic	Total N=130	Thai N=103	Foreigner N=27
Previous malaria infection	119(91.5%)	94(83%)	25(92.6%)
No	11(8.5%)	9(7%)	2(7.4%)
Yes			
Current Medication	106(81.5%)	87(84.5%)	19(70.4%)
No	24(18.5%)	16(15.5%)	8(29.6%)
Yes			

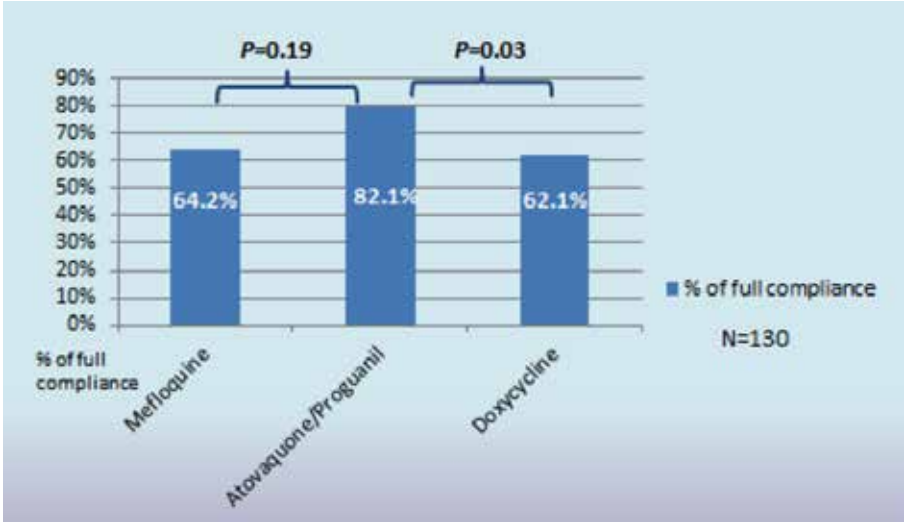

Fig 2- Comparison between drugs according to compliance

atovaquone-proguanil and doxycycline (Figure 2). The incidence of self-reported adverse effects from travelers taking chemoprophylaxis was 23.4%, which differed little between Thais and foreigners (24.6% vs 33.3%, *p*-value = 0.17). Atovaquone-proguanil had the fewest adverse effects compared with the other 2 drugs, but without statistical significance. Gastrointestinal symptoms (anorexia, nausea, vomiting, abdominal pain and diarrhea) were the most common adverse effects among all participants (16.9%), as well as in the atovaquone-proguanil (16.4%) and doxycycline groups (21.4%) (Table 2). Meanwhile, neurological symptoms (nightmare, insomnia, dizziness, and depression) were the major adverse effects in the mefloquine group (29.4%) (Table 3). Nausea was the most common adverse effect among those taking atovaquone-proguanil and doxycycline, while participants taking mefloquine experienced insomnia (Table3). Most of the adverse effects that occurred were mild, and did not interfere with the travelers' trips (Figure 3).

Travel purpose and type of chemoprophylaxis were factors associated with drug compliance (Table 4). Travel for leisure was related to better compliance than travel for work (OR 3.85, *p* -value 0.006). Participants taking atovaquone-proguanil complied better than those taking doxycycline or mefloquine (OR 2.7, *p*-value 0.01).

DISCUSSION

This study was conducted as travel-clinic-based study, in which all participants received pre-travel

Table 2 Group of adverse effects from 3 malaria chemoprophylactic drugs.

AEs	Total (N=124)	Atovaquone/ Proguanil (N=79)	Doxycycline (N=28)	Mefloquine (N=17)
GI	21 (16.9%)	13 (16.4%)	6 21.4%)	2 (11.8%)
Neurological	16 (12.9%)	6 (7.6%)	5 (17.9%)	5 (29.4%
Skin	7 (5.6%	4 (51%)	3 (10.7%)	-

Table 3 Adverse effects from malaria chemoprophylaxis reported by 124 travelers taking different drugs (6 of 130 were excluded for not taking the drug).

AEs	Total (N=124)	Atovaquone/ Proguanil (N=79)	Doxycycline (N=28)	Mefloquine (N=17)
Insomnia	6 (4.6%)	1 (1.3%)	2 (14.2%)	3 (17.6%)
Nightmare	5 (3.8%)	2 (2.5%)	1 (3.5%)	2 (11.8%)
Headache	4 (3.1%)	2 (2.5%)	1 (3.5%)	1 (5.9%)
Dizziness	4 (3.1%)	3 (3.8%)	1 (3.5%)	-
Depression	1 (0.8%)	-	1 (3.5%)	-
Anorexia	3 (2.3%)	3 (3.8%)	-	-
Nausea	8 (6.2%)	4 (5%)	3 (10.7%)	1 (5.9)
Vomiting	1 (0.8%)	1 (1.3%)	-	-
Abdominal-pain	5 (3.9%)	3 (3.8%)	2 (3.5%)	-
Diarrhea	4 (3%)	2 (2.5%)	1 (7%)	1 (5.9%)
Oral ulcer	3 (2.3%)	2 (2.5%)	-	1 (5.9%)
Rash	6 (4.6%)	4 (5%)	2 (3.5%)	-
Photo-sensitivity	1 (2.8%)	-	1 (3.5%)	-
Vaginal discharge	-	-	-	-
Other	1 (0.8%)	1 (1.3%)	-	-

counseling regarding malaria symptoms, use of chemoprophylaxis, and mosquito prevention. Our study demonstrated that most travelers complied well. This correlated with previous travel-clinic-based studies, showing that 80-90% of travelers had full compliance (Carme B *et al*, 1997; Ling J *et al*, 2002; Soto J *et al*, 2006). However, the percentage of good compliance was different in studies surveyed outside the healthcare center, which recruited interviewees from those who received pre-travel counseling and those who did not. These studies showed compliance rates of only 55-70% (Chatterjee S *et al*, 1999; Croft AM *et al*, 2001; Steffen R *et al*, 1990). The study found that Thai travelers had similar compliance rates to the foreign travelers (73.8% vs 81.5%, p-value = 0.4). Compliance was similar to a travel-clinic-based study of Japanese travelers taking mefloquine, in which 72% completed the full course of the drug (Mizuno Y *et al*, 2009); however, one study

Table 4 Factors associated with compliance (N=130).

Factors	Compliant	Noncompliant	OR	P value
Sex				
Male	68.7%	31.3%		
Female	82.5%	17.5%	2.16(1.06-4.95)	0.07
Age				
<=30	79.3%	20.7%	1.33(0.49-3.62)	0.58
>30	74.2%	25.8%		
Travel purpose				
Leisure	80.5%	19.5%	3.85(1.55-9.57)	**0.006**
(Backpack+ Group tour)				
Business	90.0%	10.0%	8.4(0.94-75.1)	0.06
Work	48.3%	51.7%		
Duration of travel				
<=10 days	80%	20%	1.71(0.77-3.83)	0.19
>10 days	70%	30%		
Drug				
Atovaquone /Proguanil	82.1%	17.9%	2.7(1.19-6.11)	**0.01**
Doxycycline /Mefloquine	63.0%	37.0%		
Previous prophylaxis				
No	76.5%	23.5%	1.28(0.52-3.14)	0.6
Yes	71.9%	28.1%		
History of malaria				
No	73.1%	26.9%		
Yes	100%	-		
Mosquito protection				
No	85.7%	14.3%	2.1(0.44-9.9)	0.52
Yes	74.1%	25.9%		
Current medication				
No	76.4%	23.6%	1.33(0.5-3.58)	0.57
Yes	70.8%	9.2%		

showed a difference, whereby less than half completed chemoprophylaxis (Matsumura T *et al*, 2005). No previous research among Asian travelers regarding the use of the same 3 chemoprophylactic drugs as our study are available for comparison.

The common reasons for noncompliance in previous studies were fear of adverse events, experiencing adverse events, and no perceived risk (Landry P *et al*, 2006; Resseguier N *et al*, 2010). In the present study, perceived uselessness of the drug was the most frequently self reported reason for noncompliance (46.9%), followed by forgetting to take the drug.

Determinants of good compliance were travel associated with tourism and taking atovaquone-proguanil. Non-tourist travel was found associated with noncompliance in a European study (Hans O *et al*, 2001). In our study, those who traveled for work purposes had poorer compliance than the other travelers. One factor that could explain this may

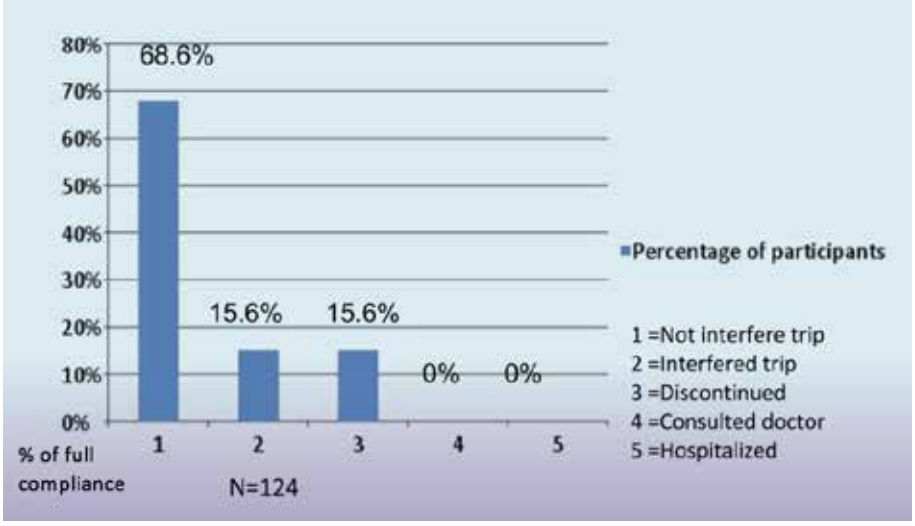

Fig 3- Severity of adverse effects.

be educational level, which might differ between workers and travelers. This may have resulted in lower risk perception of malaria and attention to the use of chemoprophylaxis. Nevertheless, the present study found no association with educational level. Taking atovaquone-proguanil, which is a daily regimen, was associated with good drug adherence, although some previous studies found that a weekly drug regimen yielded better compliance (Hans O *et al*, 2001). This may be because atovaquone-proguanil was usually the choice for short-term travelers, and duration of travel was found to be associated with chemoprophylaxis adherence (Chatterjee S *et al*, 1999; Hans O *et al*, 2001). Moreover, atovaquone-proguanil had the lowest drug withdrawal rate compared with the other chemoprophylaxes (Kato T *et al*, 2013; Schlagenhauf P *et al*, 2003). There was no significant difference in terms of gender, age, duration of travel, use of mosquito protection, previous use of malaria chemoprophylaxis, or history of malaria infection, among the compliant and noncompliant groups, which contrasted with previous studies (Chatterjee S *et al*, 1999; Frickmann H *et al*, 2013; Landry P *et al*, 2006; Hans O *et al*, 2001; Resseguier N *et al*, 2010). This may be due to the sample size being too small in the preliminary analysis.

Atovaquone-proguanil was shown to have the lowest incidence of adverse effects, as in many previous studies (Jacquerioz FA *et al*, 2009; Kato T *et al*, 2013; Schlagenhauf P *et al*, 2003). The most common adverse effect of atovaquone-proguanil and doxycycline was gastrointestinal symptoms, which concurred with previous studies (Schlagenhauf P *et al*,2003; Høgh B *et al*,2000;Kato T *et al*, 2013;Zonmes A *et al*, 2005).

Like other studies, mefloquine was found to have highest incidence of neuropsychiatric adverse effects, when compared with the other drugs (Jacquerioz FA *et al*, 2009; Kato T *et al*, 2013; Petersen E *et al*, 2000; Schlagenhauf P *et al*, 2003). However, most of the adverse effects were usually mild and tolerated by the travelers.

Our preliminary study had some limitations. First, the participant numbers were insufficient to demonstrate significant results for some factors, as shown in other studies. Second, the proportion of Thai and foreign travelers in this study differed markedly due to the greater number of Thai travelers visiting the travel clinic. Furthermore, the follow-up rate for the foreign travelers was lower than the Thais. Third, because the recorded adverse effects were self-reported, we did not verify whether the symptoms reported as adverse effects by travelers were associated with the drug,

or not. Therefore the incidence of actual adverse effects related to the drugs might be different.

In conclusion, our preliminary study provided incidence of malaria chemoprophylaxis compliance among Thai travelers as well as factors associated with good compliance and the adverse effects of 3 drugs commonly used for chemoprophylaxis in Thailand. A more complete study with more participants should yield a clearer understanding.

ACKNOWLEDGEMENT

I would like to thank all my advisors, especially for their guidance and support. I also wish to thank all travel clinic nurses and my colleagues who helped me throughout the data-collection process. Finally, I am very grateful to all of the participants, who agreed to participate in the study and for their excellent cooperation. Financial support is acknowledged from the Faculty of Tropical Medicine, Mahidol University.

REFERENCES

Bradley DJ, Warhurst DC. Malaria prophylaxis: guidelines for travelers from Britain. *BMJ* 1995;310:709–14.

Carme B, Peguet C, Nevez G. Compliance with and tolerance of mefloquine and chloroquine + proguanil malaria chemoprophylaxis in French short-term travellers to sub-Saharan Africa. *Trop Med Int Health* 1997;2:953–6.

Chatterjee S. Compliance of Malaria Chemoprophylaxis among Travelers to India. *J Travel Med* 1999;6:7–11.

Croft AM, Garner P. Review: mefloquine prevents malaria but has adverse effects that limit its acceptability in adults not immune to malarial infection. *Evidence Based Medicine* 2001;6(5):143.

Frickmann H, Schwarz NG, Holtherm HU, *et al*. Compliance with antimalarial chemoprophylaxis in German soldiers: a 6-year survey. Infection 2013;41(2):311-20.

Hoebe C, de Munter J, Thijs C. Adverse effects and compliance with mefloquine or proguanil antimalarial chemoprophylaxis. *Eur J Clin Pharmachol* 1997;52:269-75.

Høgh B, Clarke PD, Camus D, *et al*. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. The Lancet 2000;356(9245):1888-94

Jacquerioz FA, Croft AM. Drugs for preventing malaria in travelers. *Cochrane database syst Rev* 2009 Oct 7;(4):CD006491.

Kitchener SJ, Nasveld PE, Gregory RM, Edstein MD. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. *Med J Aust* 2005;182:168–71.

Ling J, Baird JK, Fryauff DJ, *et al*. Randomized, Placebo-Controlled Trial of Atovaquone/ Proguanil for the Prevention of Plasmodium falciparum or Plasmodium vivax Malaria among Migrants to Papua, Indonesia. Clin Infect Dis 2002;35(7):825-33.

Lobel HO, Baker MA, Gras FA, *et al*. Use of Malaria Prevention Measures by North American and European Travelers to East Africa. J Travel Med 2001;8(4):167-72.

Matsumura T, Fujii T, Miura T, *et al*. Questionnaire-based analysis of mefloquine chemoprophylaxis for malaria in a Japanese population. J Infect Chemother 2005 Aug;11(4):196-8

MizunoY, Kudo K, Kano S. Mefloquine chemoprophylaxis against malaria in Japanese travelers: results of a study on adverse effects. *Tropical Med Health* 2010;38:103-6.

Petersen E, Ronne T, Ronn A, *et al*. Reported side effects to chloroquine, chloroquine plus proguanil, and mefloquine as chemoprophylaxis against malaria in Danish travelers. J Travel Med 2000;7(2):79-84.

Resseguier N, Machault V, Ollivier L, *et al*. Determinants of compliance with malaria

chemoprophylaxis among French soldiers during missions in inter-tropical Africa. Malaria Journal 2010;9:41.

Ryan ET, Kain KC. Health Advice and Immunizations for Travelers. *N Engl J Med 2000*;342:1716-25.

Sonmez A, Harlak A, Kilic S, *et al*. The efficacy and tolerability of doxycycline and mefloquine in malaria prophylaxis of the ISAF troops in Afghanistan. J Infect 2005;51:253-8.

Soto J, Toledo J, Luzz M, *et al*. Randomized, double-blind, placebo-controlled study of Malarone for malaria prophylaxis in non-immune Colombian soldiers. Am J Trop Med Hyg 2006;75:430-3.

Steffen R, Heusser R, Mächler R, *et al*. Malaria chemoprophylaxis among European tourists in tropical Africa: use, adverse reactions, and efficacy. Bull World Health Organ 1990;68(3):313-22.

Tan KR, Magill AJ, Parise ME, Arguin PM. Doxycycline for Malaria Chemoprophylaxis and Treatment: Report from the CDC Expert Meeting on Malaria Chemoprophylaxis. *Am J Trop Med Hyg* 2011;84(4):517-31.

Wilson ME, Weld LH, Boggild A, *et al*. Fever in Returned Travelers: Results from the GeoSentinel Surveillance Network. Clin Infect Dis 2007;44:2560-8.