Tropical Medicine and Health Vol. 38 No. 3, 2010, pp. 103-106

Original article

Mefloquine chemoprophylaxis against malaria in Japanese travelers: results of a study on adverse effects

Yasutaka Mizuno[1], Koichiro Kudo[1] and Shigeyuki Kano[2*]

Received 13 October, 2009 Accepted 29 July, 2010 Published online 28 August, 2010

Abstract: Although Mefloquine is commonly used as a prophylactic drug for travelers to malaria endemic areas, there are only limited reports about its adverse effects in Japanese travelers. We carried out a prospective observation study of 107 travelers who were prescribed mefloquine as chemoprophylaxis against malaria prior to their departure from November 2004 to October 2006. We carefully sought the appropriate prescription for each client according to the guidelines for Japanese overseas travelers. The clients consisted of 71 men and 36 women of whom we were able to follow 65 travelers until the end of their prophylactic procedure. Of the 65, 47 travelers completed their full course of chemoprophylaxis. Different adverse effects were reported in 19 travelers of them such as fatigue (n=9), dizziness (n=6), headache (n=3), nausea (n=3), drowsiness (n=2), strange dreams (n=2), anxiety (n=2), fever (n=1) and skin rash (n=1). Three travelers were incapable of continuing chemoprophylaxis due to the adverse effects, but no serious events were noted. Through our study, mefloquine chemoprophylaxis seemed tolerable for Japanese travelers. We believe that our detailed consultation and careful monitoring reduced the incidence of severe adverse effects and maintained the high rate of adherence to chemoprophylaxis.
Key words: malaria, mefloquine, chemoprophylaxis, Japanese travelers, adverse effects

INTRODUCTION

Malaria is a serious health problem among travelers to endemic countries. Approximately 25 to 30 million international travelers visit malarious areas each year, and the number of the imported malaria cases has been rising [1]. Antimalarial chemoprophylaxis is the main preventive measure proposed to international travelers who are willing to protect themselves. Mefloquine (MQ), which has been available in Europe since 1985 and in the United States since 1990 [2], is commonly prescribed for travelers to areas where chloroquine resistant malaria is endemic [3]. However, MQ was not licensed for use specifically against malaria nor registered in Japan until 2001, mainly because only a small number of malaria cases were reported in this country [4]. Indeed, the significance of chemoprophylaxis is not well-recognized in Japan by either travelers or medical practitioners. Therefore, aside from the prophylactic usage of MQ in Japan Ground Self-Defense Force members [5,6] and overseas travelers, few studies have been conducted on the adverse effects (AEs) [7]. In this report, we analyzed MQ chemoprophylaxis in the Japanese travelers who visited the travel clinic at the International Medical Center of Japan (IMCJ).

METHODS

We carried out a prospective observation study in 107 travelers who were given MQ as chemoprophylaxis in our travel clinic in the IMCJ prior to their departure from Japan. The study period was November 2004 through October 2006. The IMCJ is a government hospital which has the largest travel clinic in Japan. Around 400-500 overseas travelers come to the clinic annually before commencing their overseas travel. The study group consisted of 71 men (66.4%) and 36 women (33.6%) ranging in age from 18 to 64 (mean age 29.2) years.

Information obtained from these travelers included the date of departure, the purpose of their travels, such as business, leisure or visiting friends and relatives (VFRs), as well as the duration of their visits and places to be visited. With this information, we provided prescriptions for the travelers

[1] Disease Control and Prevention Center, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku, Tokyo, 162-8655 Japan
[2] Research Institute, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku, Tokyo, 162-8655 Japan
*Corresponding author:
E-mail: kano@ri.ncgm.go.jp
Tel: +81-3-3202-7181
Fax: +81-3-3202-7364

in careful accordance with the guidelines on the prevention of malaria for Japanese overseas travelers [8]. Travelers were followed up by telephone or fax to assess their adherence to the MQ prescription and to assess if there were any AEs during and after completion of the prescribed schedule. The travelers were advised beforehand to contact us if any severe AEs had occurred.

RESULTS

The majority of travelers (83.1%) planned to stay overseas for less than 1 month. As for the purpose of travel, 24% were sightseeing, 14% backpacking, 5% visiting friends and relatives (VFRs), 33% traveling for research, 10% for office work, 11% for volunteer work, and 3% for study. The most frequent destination was Indonesia followed by Kenya and Tanzania (Table 1).

Out of the 107 travelers, 65 could be followed up throughout the course of their prophylactic treatment. Out of the 65, 47 (72.3%) continued their course of chemoprophylaxis until 4 weeks after returning to Japan, while the other 16 (24.6%) travelers inadvertently withdrew from the prophylactic procedure earlier than scheduled. The remaining 2 travelers (3.1%) did not take MQ at all despite the advised chemoprophylaxis.

Different types of AEs were reported by 19 travelers,

Table 1: Travel Destinations

Asia (N=44)	
Indonesia	25
India	8
Philippines	4
Thailand	1
Cambodia	1
Around Asia	5
Africa (N=72)	
Kenya	19
Tanzania	9
Ghana	8
Senegal	6
Mali	5
Zimbabwe	5
Burkina Faso	3
Madagascar	3
Ethiopia	2
Congo	2
Somaliland	2
Rwanda	2
Around Africa	3
Oceania (N=6)	
Papua New Guinea	6

Table 2: Types and duration of adverse effects

No.	Age	Sex	Types of adverse effects									Duration	Adherance
			Fa	Di	H	N	Dr	A	SD	Fe	R		
1	27	M	●									Persist 4-5 weeks	Completed
2	37	M							●			1 day after 1st dose	Completed
3	30	M				●						1 day after 1st dose	Completed
4	28	F		●								1 day after 1st dose	Completed
5	32	F	●	●					●			1 day after every dose	Withdrew 2 doses left
6	23	M	●		●							Persist 3-4 weeks	Withdrew 1 dose left
7	27	F					●					Persist 1-2 weeks	Withdrew 2 doses left
8	24	M	●		●							3 days after 1st dose	Completed
9	24	F	●		●							4 days after 1st dose	incapacitated *
10	40	M		●						●	●	1 day after 1st dose	incapacitated
11	32	M	●									1 day after 1st dose	Completed
12	37	F				●						1 day after 5th dose	Completed
13	40	M	●									1 day after 1st dose	incapacitated
14	41	F						●				2-3 days after 2nd dose	Withdrew 1 dose left
15	25	M		●								1 day after 1st dose	unkown
16	32	M		●			●					3 day after 1st dose	unkown
17	26	F						●				2 day after 1st dose	unkown
18	28	F	●									1 day after 1st dose	unkown
19	64	M	●	●		●						persist completed	Completed

Fa: Fatigue, Di: Dizziness, H; Headache, N; Nausea, Dr; Drowsiness, A; Anxiety, SD; Strange dream, Fe; Fever >38.5℃, R; Skin rash
* incapacitated : incapable of continuing prophylaxis due to AEs

such as fatigue (n=9), dizziness (n=6), headache (n=3), nausea (n=3), drowsiness (n=2), anxiety (n=2), strange dreams (n=2), fever (n=1) and skin rash (n=1) (Table 2). Of the 16 travelers who withdrew from the procedure, 9 suffered no AEs but inadvertently terminated chemoprophylaxis, while 7 suffered AEs, including 3 individuals who were incapable of continuing chemoprophylaxis due to one or a mixture of their first episodes of AEs such as general fatigue, headache, fever, or skin rash. The remaining 4 travelers with AEs terminated the course inadvertently (with only 1 or 2 more doses left), according to our interview (Table 2). No serious events that might threaten the life of the clients or cause severe disability were reported in this study.

DISCUSSION

The safety and tolerability of MQ for chemoprophylaxis is a subject of controversy mainly due to reports of neuropsychiatric symptoms and other MQ-associated AEs. A review of studies showed that the incidence of AEs during the use of MQ lay in the range of 12% to 90% and was usually equivalent to the incidence reported for other chemoprophylactic regimens [9]. In fact, many clients who visited our clinic worried about AEs due to MQ and some refused to take it. However, the results of the present study show that the incidence of AEs was relatively low, that the AEs were not associated with any serious events, and that the adherence rate was quite high.

In analyzing AEs, individual characteristics such as race, gender, underlying diseases, and the behavior and personality of users should be kept in mind [10]. In addition, the precise mode of MQ that causes neuropsychiatric AEs is difficult to define. The possibility of travel as a catalyst for such events should be considered, together with other confounding factors such as the use of recreational drugs, alcohol, and various environmental factors including stress from international travel, change of climate, or arduous undertakings might also play a part [11]. In the present study, we advised clients to start taking MQ 2-3 weeks before their departure and monitor AEs very carefully, because the AEs of MQ usually occur within the first three doses [12].

In separate Japanese studies on healthy Self-Defense Force members, the total incidence of AEs was 33% in Mozambique [5] and 24% in East Timor [6]. Both reports indicated that MQ chemoprophylaxis was generally well tolerated among the subjects, but whether or not this tolerability is similar among ordinary Japanese travelers remains unclear. In another questionnaire-based study, an extremely high incidence of AEs (75%, i.e. 12 of 16 travelers) was reported among Japanese travelers [7]. In this study, the authors collected the answers to the questionnaire from MQ users only by letter and without any personal interview.

Our study showed a 35% incidence of AEs and good adherence to the MQ treatment. Although the number of subjects in our study was limited as compared to those reported from abroad, MQ chemoprophylaxis seemed quite tolerable for Japanese travelers. In addition, we believe that accurate consultation for travelers regarding the risk of malaria leads to good adherence to chemoprophylaxis regimens. Fortunately, in our study, no one suffered from malaria during or after their travel with or without chemoprophylaxis. Now that MQ resistant malaria is reported widely in Southeast Asia, we need to propose alternative chemoprophylactic regimens such as atovaquone/proguanil or doxycycline in the guidelines [8]. It is also noteworthy that these prophylaxes were reported to be less associated with neuropsychiatric AEs than MQ [13,14].

In this report, the importance of MQ prophylaxis is discussed with reference to the frequency and severity of AEs and other risks. However, the benefits of MQ prophylaxis should also be widely discussed, particularly in Japan, where no other registered antimalarial drug for prophylactic usage is available. Although the annual number of imported malaria cases has been decreasing for the last decade owing partly to the increased use of proper MQ prophylaxis by travelers, many severe cases of falciparum malaria including some fatal cases, are still being reported [15]. The usefulness of MQ prophylaxis should be assessed on the basis of a balance between risk and benefit.

ACKNOWLEDGMENTS

This study was supported in part by a Grant for International Medical Research (21A107) from the Ministry of Health, Labour and Welfare of Japan.

REFERENCES

1. Muentener P., Schlagenhauf P. and Steffen R. (1999). Imported malaria (1985-95): trends and perspectives. *Bull. World Health Organ.* 77: 560-6.
2. Schlagenhauf P. (1999). Mefloquine for malaria chemoprophylaxis 1992-1998: a review. J. Travel Med. 6: 122-33.
3. Connor B. A. (2001). Expert recommendations for antimalarial prophylaxis. J. Travel Med. 8 (Supple 3): S57-64.
4. Kano S. and Kimura M. (2004). Trends in malaria cases in Japan. Acta Trop. 89: 271-8.
5. Takeshima S. (1994). Side effects with mefloquine for long term malaria prophylaxis. Jpn. J. Trop. Med. Hyg. 22: 185-92.
6. Fujii T., Kaku K., Jelinek T., Kimura M. (2007) Malaria and mefloquine prophylaxis use among Japan Ground Self-Defense Force personnel deployed in East Timor. J. Travel.

Med. 14:226-32.
7. Matsumura T., Fujii T., Miura T., Koibuchi T., Endo T., Nakamura H., Odawara T., Iwamoto A. and Nakamura T. (2005) Questionnaire-based analysis of mefloquine chemoprophylaxis for malaria in a Japanese population. J. Infect. Chemother.11:196-8.
8. Mizuno Y., Kudo K. I., and Kano S. (2006) Chemoprophylaxis according to the guidelines on malaria prevention for Japanese overseas travelers. Southeast Asian J. Trop. Med. Pub. Health 37(supple 3): 11-4.
9. Schlagenhauf P. (2001) Traveler's malaria. (Schlagenhauf ed.) BC Decker Inc. Hamilton Ontario, Canada. 188-209.
10. Schlagenhauf P. and Steffen R. (2000) Neuropsychiatric events and travel: do antimalarials a play role? J. Travel Med. 7: 225-6.
11. Meier CR., Wilcock K., Jick SS. (2004) The risk of severe depression, psychosis or panic attacks with prophylactic antimalar Drug. Safials. 27:203-13.
12. Bradley D. and Bannister B. (2003) Guidelines for malaria prevention in travellers from the United Kingdom for 2003. Commun. Dis. Pub. Health 6:180-99.
13. Overbosch D., Schilthuis H., Bienzle U., et al.(2001) Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double blind study. Clin. Infect. Dis. 33:1015-21.
14. Schlagenhauf P., Tschopp A., Johnson R., et al. (2003) Tolerability of malaria chemoprophylaxis in non-immune travelers to sub-Saharan Africa: multicentre, randomized, double blind, four arm study. BMJ. 327:1078-81.
15. Kano S. (2010) Artemisinin-based combination therapies and their introduction in Japan. J. Infect. Chemother. Epub ahead of print, June 10.