Journal of Travel Medicine

International Society of Travel Medicine
Established 1991
Promoting healthy travel worldwide

Journal of Travel Medicine, 2016, 1–5
doi: 10.1093/jtm/taw064
Original Article

Original Article

Effectiveness of twice a week prophylaxis with atovaquone–proguanil (Malarone®) in long-term travellers to West Africa

Tamar Lachish, MD[1,*], Maskit Bar-Meir, MD[1], Neta Eisenberg, MD[2], and Eli Schwartz, MD[3,4]

[1]The Infectious Diseases Unit, Shaare-Zedek Medical Center, P.O.B 3235, Jerusalem 91301, Israel, [2]Centro Médico La Paz, Malabo, Equatorial Guinea, [3]The Center for Geographic Medicine, the Chaim Sheba Medical Center, Tel-Hashomer, Israel, and [4]Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel

* To correspondence should be addressed: Tel: +972-2-6666340, Fax: +972-2-6666840; Email: lachisht@yahoo.com
The paper was presented as an oral presentation in the CISTM14 2015, Quebec, Canada and the APTHC 2016, Kathmandu, Nepal.

Submitted 1 July 2016; revised 16 August 2016; Accepted 23 August 2016

Abstract

Background: Current guidelines recommend daily dosing of atovaquone–proguanil (AP), beginning a day before travel to endemic areas and continuing for 7 days after departure. Adherence of long-term travellers to daily malaria chemoprophylaxis tends to be poor, even when residing in highly endemic malaria regions. Evidence from a volunteer challenging study suggests that non-daily, longer intervals dosing of AP provides effective protection against Plasmodium *falciparum*. This study examines the effectiveness of twice weekly AP prophylaxis in long-term travellers to highly endemic *P. falciparum* areas in West Africa.

Methods: An observational surveillance study aimed to detect prophylactic failures associated with twice weekly AP, during the years 2013–2014, among long-term expatriates in two sites in West Africa. The expatriates were divided according to the malaria prophylaxis regimen taken: AP twice weekly; mefloquine once weekly and a group refusing to take prophylaxis. Malaria events were recorded for each group. The incidence-density of malaria was calculated by dividing malaria events per number of person-months at risk.

Results: Among 122 expatriates to West Africa the malaria rates were: 11.7/1000 person-months in the group with no-prophylaxis ($n = 63$); 2.06/1000 person-months in the 40 expatriates taking mefloquine ($P = 0.006$) and no cases of malaria (0/391 person-months, $P = 0.01$) in the twice weekly AP group ($n = 33$).

Conclusions: No prophylaxis failures were detected among the group of expatriates taking AP prophylaxis twice weekly compared with 11.7/1000 person-months among the no-prophylaxis group. Twice weekly AP prophylaxis may be an acceptable approach for long-term travellers who are unwilling to adhere to malaria chemoprophylaxis guidelines.

Key words: Atovaquone–proguanil, mefloquine, malaria chemoprophylaxis, travellers, expatriates

Background

Malaria is a potentially preventable life threatening disease that affects tropical and subtropical areas.[1] There are currently 97 countries with continuing risk of malaria transmission. These destinations are visited by more than 125 million international travellers each year.[2] The travellers' risk of contracting malaria is highly variable from country to country and even between areas within the same country. Furthermore, the risk is also affected by seasonality, the specific itinerary and the planned activities. At least 10 000 cases of travel-associated malaria occur annually. Most of these cases occur in travellers that did not adhere to protective measures or usage of malaria chemoprophylaxis.[2] It is important to note that malaria is still the leading cause of hospitalization in febrile ill-returning travellers and it is

the leading cause of death due to an infectious disease among travellers.[3]

Globally, most malaria cases and deaths occur in sub-Saharan Africa due to a heavy burden of *Plasmodium falciparum* malaria, and therefore, all travellers to this region should ideally take chemoprophylaxis. Three main options for chemoprophylaxis are available for travellers to *P. falciparum* endemic areas in sub-Saharan Africa: mefloquine, doxycycline and atovaquone–proguanil (AP). These options differ in their dosing regimen, cost and side effect profile. Adherence to chemoprophylaxis varies among different series of travellers, but in general it is unsatisfactory especially among long-term travellers and expatriates.[4–9]

Long-term travellers pose even a greater challenge regarding malaria chemoprophylaxis, not only because of their longer exposure but also due to special activities (i.e. working outdoors in highly endemic areas); different living conditions; the cost of a prolonged prophylactic regimen and side effects of long-term medications usage.[10]

AP demonstrates consistently high protective efficacy against *P. falciparum* with an excellent safety profile during both prophylaxis and treatment courses, with severe adverse events rarely reported.[11–13] Despite the favourable adverse effect profile and the relatively ease of take, travellers are yet reluctant to adhere to AP chemoprophylaxis, mainly due to cost considerations, but also due to unwillingness to take medications on regular daily basis.[9,14] The half-life of atovaquone is long, ranging from about 50 to 84 h. The half-life of proguanil is 14–20 h.[15] Yet, current guidelines recommend daily dosing of AP, beginning a day before travel to an endemic area and continuing for 7 days after departure. Despite further evidence from previous volunteer studies suggesting that a single-dose of AP provides indeed effective chemoprophylaxis against *P. falciparum* challenge at dosing intervals supportive of weekly dosing,[16,17] no clinical studies have attempted to test the effectiveness of a prolonged interval of AP regimen. Weekly mefloquine could theoretically be an attractive choice for long-term travellers; however, it has a problematic reputation due to its adverse events profile augmented by a recent black-box labelling of the drug.[18]

The aim of this study was to assess the efficacy of twice weekly AP regimen in high-risk groups travelling to West Africa and refusing to take daily malaria chemoprophylaxis or once weekly mefloquine.

Patients and Methods

Study Design

To detect prophylactic failures associated with twice weekly AP, we conducted an observational surveillance during the years 2013–2014 among long-term expatriates in two sites in West Africa. Living conditions were similar in each site.

The study was approved by the Sheba Medical Center Institutional Ethical Review Board.

Patient Population

Long-term expatriates (≥6 months), travelling to work in West Africa—either working in the jungles of Angola or as medical staff at the Centro Médico La Paz, Malabo, Equatorial Guinea. All expatriates were recommended personally to adhere to malaria chemoprophylaxis (AP or mefloquine) according to the approved manufacturers' regimen for each drug. The group staying in Angola decided not to take any chemoprophylaxis and after 6 months connected us for advice due to high occurrence of malaria among the group members. Despite their high malaria attack rate they still refused taking chemoprophylaxis according to the recommended protocols, but agreed for twice weekly AP (starting one day before entering malaria endemic areas), that was offered assuming it is better than no treatment at all, and as a last-resort attempt to reduce malaria incidence.

This option was attractive also for expatriates working in Malabo, Equatorial-Guinea, while others still refused taking any chemoprophylaxis.

This sequence of events provided us with unique opportunity to compare the effectiveness of twice weekly AP to currently recommended regimens, or to no prophylaxis. Thus, avoiding the ethical considerations may prevent the design of a prospective randomized controlled trial.

In Angola, adherence to prophylaxis was based on direct observed therapy (AP twice a week was handed out by a paramedic). In Equatorial Guinea, adherence was based on self-reporting of the medical staff.

The expatriates from the two destinations were divided into three groups according to the malaria chemoprophylaxis they took—Mefloquine once weekly; AP twice weekly; and no chemoprophylaxis. Malaria events were recorded for each group. The incidence rate of malaria was compared between the groups by rate difference. Confidence intervals (CI) are presented for all rates. A logistic regression model was used to analyse the protective effect of either treatment against malaria, after adjusting for gender and location (Angola vs Equatorial Guinea).

The statistical analysis was done with SPSS 19.0 and WINPEPI version 11.9.

Results

A group of 14 expatriates (all males, median age 24 years) working in the jungles of Angola remained there for 16 months (1 January 2012–30 April 2013)— the whole period in the same living conditions. During the first 6 months they all refused taking malaria chemoprophylaxis and accordingly eight cases of malaria were documented, all during the heavy rainy season of that area (January through April)—two severe cases that were diagnosed and treated in a western medical facility in Luanda (a positive Rapid diagnostic test and a positive blood film); six cases of acute onset of fever had a positive blood film in a local medical facility and had a dramatic response to therapeutic doses of mefloquine. Despite this high incidence of malaria, the expatriates yet refused taking once weekly mefloquine or AP on regular daily basis. They were consequently offered to take the twice weekly AP regimen, which they all accepted. During the next 10 months of their stay in the same facility, including again the heavy rainy season, no cases of fever or malaria were documented.

One hundred and eight medical staff and their family members (M:F ratio 1:1; age range 1.5–71 years; 28 of 107 were ≤12 years old) lived for different periods (median stay = 19.45 months) with same living condition, at the Centro Médico La Paz, Malabo, Equatorial Guinea. As medical

personal they all had knowledge regarding the malaria risk and consequences and received pre-travel consultation that advised them and their family members to take malaria chemoprophylaxis, yet, almost a half of them ($n = 49$) chose not to take any chemoprophylaxis. Forty medical staff members or their families received standard prophylaxis with mefloquine. The remaining medical staff ($n = 19$) heard from each-other about the experience with twice a week AP of the group from Angola and decided on their own to take the same protocol.

Altogether, 122 expatriates to West Africa were included in this study. The 14 expatriates to Angola contributed person-time twice; first to the no-prophylaxis group and then to the twice weekly AP group. Overall, 63 subjects were included in the group that did not take any malaria chemoprophylaxis; 40 took mefloquine according to the recommended regimen; and 33 took AP twice weekly (Figure 1). None of the expatriates chose to take the once daily AP according to the manufactures' recommendation or doxycycline.

Altogether, there were 1368 person-months of follow-up for the no-prophylaxis group, 983 person-months and 391 person-months for the mefloquine and the twice-weekly AP groups, respectively (Figure 1).

Malaria incidence was significantly lower in both the mefloquine (2 per 1000 person months, 95% CI 1.5–37, $P = 0.006$) and in the twice weekly AP groups (0 episodes per 391 person-months, 95% CI 1.4–∞, $P = 0.01$) than in the no-prophylaxis group (11.7 episodes per 1000 person-months).

After adjusting for gender and location, either treatment was associated with ~20 times decreased odds for malaria compared with no prophylaxis: OR = 0.05(95% CI 0.006–0.42; $P = 0.006$).

All travellers taking the twice weekly AP chemoprophylaxis had an excellent compliance with this regimen and complete adherence to the protocol for the duration of their stay in the endemic area.

Discussion

Despite many years of availability, malaria chemoprophylaxis adherence is still a problematic issue. Travellers are yet reluctant to use chemoprophylaxis, and the compliance is further complicated in long-term travellers who prefer not to use any medications on a regular daily basis. Our study emphasizes this problematic issue—108 of the expatriates were medical staff or their family members, all aware of their malaria risk in a highly endemic area, and yet 45% of them chose not to take any malaria chemoprophylaxis. These low compliance rates among similar medical staff in another hospital in Equatorial Guinea have previously been reported.[19] Furthermore, data and controlled studies on long-term safety and efficacy of anti-malarial

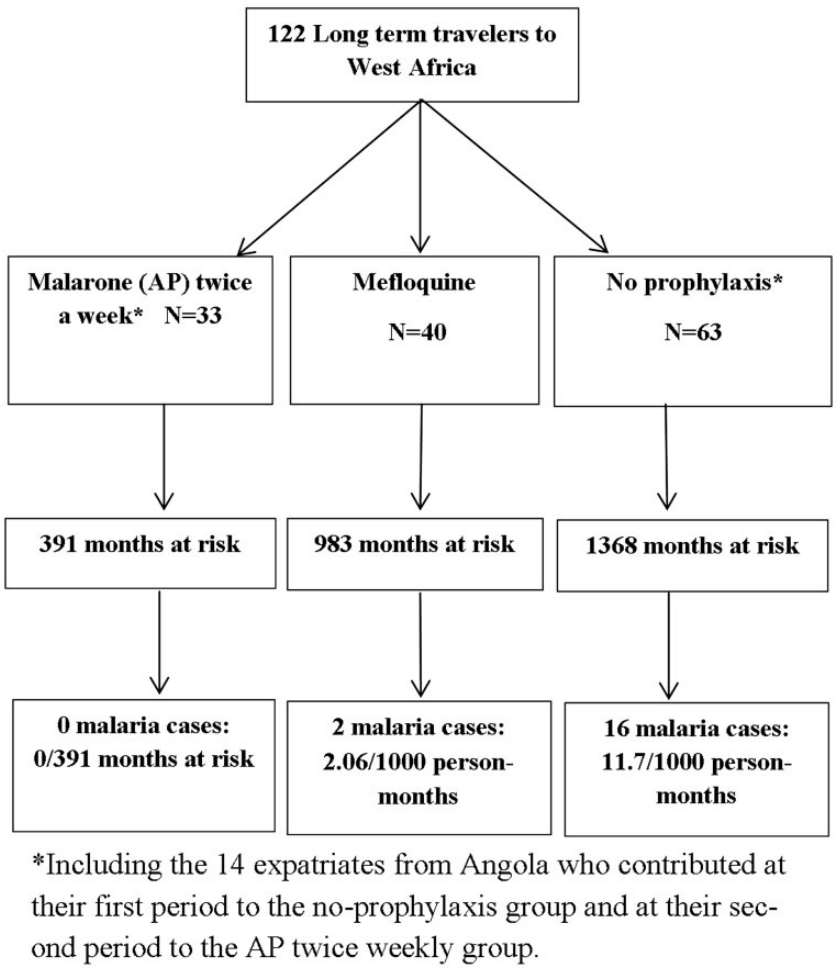

Figure 1. Malaria events according to the malaria chemoprophylaxis taken

agents are scarce.[10] Accordingly, in the GeoSentinel database long-term travellers experienced malaria more frequently compared with short-term travellers, due to poor compliance to chemoprophylaxis.[20]

Atovaquone is active against the liver stages of the malaria parasites and has a relatively long half-life (50–84 h),[15] combining it with proguanil that is also active against the liver stages, results in an efficacious prophylactic drug with a potential of more convenient dosing regimen. However, upon licensure the schedule examined was daily doses starting at day −1 pre-exposure and continuing up to day +7 after the end of exposure.[21] In this randomized, double-blind, placebo-controlled study, 12 healthy volunteers on the per-protocol prophylactic schedule of the drug were compared with 4 healthy volunteers taking placebo. Both groups were challenged with *P. falciparum* via infected mosquitoes. Four cases of malaria were documented, all in the placebo group, while no cases were recommended in the treated arm. These results led to clinical studies in immune African population which proved the efficacy of the drug to be around 98%.[22] Based on these data, AP was registered with this schedule and to be the official recommended AP prophylactic regimen including non-immune travellers.[2] In 2012, Deye *et al.*[16] published a study performed in volunteers with similar methods as the above-mentioned licensure study, but examined the prolonged protection provided by a single prophylactic dose of AP. Their goal was to examine a prolonged protection provided by a single prophylactic AP dose against a human *P. falciparum* malaria challenge. Six volunteers of the control cohort were compared with 30 volunteers of the prophylaxis cohort which were randomly assigned to one of five single-dose regimens—17 volunteers taking different doses of AP at day −7 before the challenge; 6 volunteers taking a standard dose of AP at day −1; and 5 volunteers taking a standard dose of AP at day +4 after challenge. Six malaria cases occurred among the six control cases. Three malaria cases were recorded in the treatment cohort, all in the day −7 treatment groups, while no cases were recorded in the day +4 regimen (which can be compared with twice a week regimen). Since malaria attack rate after challenge approximates 100%, even small numbers of patients suffice to demonstrate the efficacy of AP therapy. And indeed, both studies mentioned above had practically a power of 100%.

Leshem *et al.*[23] were the first to study a modification of the recommended schedule, examining the effectiveness of a short prophylactic course of AP, discontinued it 1 day (instead of 7 days) after return from a travel to Sub-Saharan Africa. Among 485 travellers (cumulative exposure of 4979 days), 421 (87%) discontinued AP 1 day after leaving the endemic region. None of the 485 travellers had malaria infection. They conclude inline with the study by Deye *et al.*[16] that ending the AP prophylaxis treatment 1 day after leaving the malaria endemic area did not compromise the drug efficacy. Furthermore, the travellers who were advised to use the short-course of prophylaxis reported a substantially higher compliance to chemoprophylaxis compared to those recommended taking the full schedule.

Given the circumstances described in the Methods we encountered a unique opportunity to examine the effectiveness of twice a week AP prophylaxis among long-term travellers to Western Africa, utilizing a quasi-experimental set-up. No prophylaxis failures were detected among the group of travellers who took AP prophylaxis twice a week (0 cases per 391 person-months), while among the group not taking any prophylaxis the incidence was 11.7/1000 person-months. The adherence to the twice weekly AP regimen was 100%, including in the 14 expatriates to Angola that were previously very reluctant to use any chemoprophylaxis regimen. These 14 travellers serve as a control group for themselves—prior to the twice weekly AP regimen >50% of them (8/14) had clinical malaria (two severe cases) within a short period of time. After commencing of this chemoprophylaxis, no malaria cases were detected during 10 months of stay in the same area with identical living conditions and throughout the highly rainy season.

The main limitations of this study are due to the 'natural experiment' design of the study; groups were self-selected and the intervention was unblinded. Furthermore, there are potential confounders such as practicing different preventive personal protection and the self-medication reporting of the medical group, but this bias is assumed to be similar in the mefloquine and the AP group. However, it is important to note that altogether the groups in both sites lived in identical living conditions with the same environmental risk factors thus allowing the comparisons between the groups.

Another main limitation of the study is that the cumulative exposure of our cohort of twice weekly AP may have been relatively small. However, all our expatriates resided in highly endemic areas of West Africa with an estimated annual rate of *P. falciparum* malaria cases of 277–375 per 100 000 travellers,[24,25] and practiced high-risk activities, and therefore malaria cases have been prevented. In fact, in our cohort among those without prophylaxis the rate of malaria was 11.7/1000 person-months, sufficient to detect malaria cases even in the group of AP users.

Furthermore, the subgroup of the 14 of the expatriates' working in the jungles of Angola, served as their own control. Despite their short cumulative exposure there was a decrease in malaria events from more than a 50% attack rate to 0 cases after starting AP twice weekly.

Conclusions

We conclude that in this study twice weekly AP was an efficacious prophylaxis regimen for long-term expatriates to highly endemic areas. The shortening of the original schedule raised the compliance to malaria chemoprophylaxis. We recommend further validation of our findings by clinical trials comparing the different AP regimens, and active surveillance in larger cohorts. Meanwhile, we feel that a twice weekly AP prophylaxis may be a reasonable approach for long-term travellers who are not adherent to current malaria chemoprophylaxis guidelines.

Conflicts of interest: None declared.

References

1. WHO. *World malaria report 2014*: World Health Organization (WHO). 2014.
2. WHO. *International Travel and Health*. ed. Malaria. Geneva: World Health Organization (WHO), 2015.

3. Leder K, Torresi J, Libman MD *et al*. Geosentinel surveillance of illness in returned travelers, 2007-2011. *Ann Intern Med* 2013; **158**: 456–68.
4. Chatterjee S. Compliance of malaria chemoprophylaxis among travelers to India. *J Travel Med* 1999; **6**: 7–11.
5. Lobel HO, Miani M, Eng T, *et al*. Long-term malaria prophylaxis with weekly mefloquine. *Lancet* 1993; **341**: 848–51.
6. Hopperus Buma AP, van Thiel PP, Lobel HO, *et al*. Long-term malaria chemoprophylaxis with mefloquine in Dutch marines in Cambodia. *J Infect Dis* 1996; **173**: 1506–9.
7. Sanchez JL, Bendet I, Grogl M, *et al*. Malaria in Brazilian military personnel deployed to Angola. *J Travel Med* 2000; **7**: 275–82.
8. Whitman TJ, Coyne PE, Magill AJ, *et al*. An outbreak of *Plasmodium falciparum* malaria in U.S. Marines deployed to Liberia. *Am J Trop Med Hyg* 2010; **83**: 258–65.
9. Landman KZ, Tan KR, Arguin PM. Knowledge, attitudes, and practices regarding antimalarial chemoprophylaxis in U.S. Peace corps volunteers—Africa, 2013. *MMWR Morb Mortal Wkly Rep* 2014; **63**: 516–7.
10. Chen LH, Wilson ME, Schlagenhauf P. Prevention of malaria in long-term travelers. *JAMA* 2006; **296**: 2234–44.
11. Boggild AK, Parise ME, Lewis LS, Kain KC. Atovaquone-proguanil: report from the CDC expert meeting on malaria chemoprophylaxis (II). *Am J Trop Med Hyg* 2007; **76**: 208–23.
12. Nakato H, Vivancos R, Hunter PR. A systematic review and meta-analysis of the effectiveness and safety of atovaquone proguanil (malarone) for chemoprophylaxis against malaria. *J Antimicrob Chemother* 2007; **60**: 929–36.
13. Nicosia V, Colombo G, Consentino M, *et al*. Assessment of acceptability and ease of use of atovaquone/proguanil medication in subjects undergoing malaria prophylaxis. *Ther Clin Risk Manag* 2008; **4**: 1105–10.
14. Senn N, D'acremont V, Landry P, Genton B. Malaria chemoprophylaxis: what do the travelers choose, and how does pretravel consultation influence their final decision. *Am J Trop Med Hyg* 2007; **77**: 1010–4.
15. Nixon GL, Moss DM, Shone AE, *et al*. Antimalarial pharmacology and therapeutics of atovaquone. *J Antimicrob Chemother* 2013; **68**: 977–85.
16. Deye GA, Miller RS, Miller L, *et al*. Prolonged protection provided by a single dose of atovaquone-proguanil for the chemoprophylaxis of *Plasmodium falciparum* malaria in a human challenge model. *Clin Infect Dis* 2012; **54**: 232–9.
17. Shapiro TA, Ranasinha CD, Kumar N, Barditch-Crovo P. Prophylactic activity of atovaquone against *Plasmodium falciparum* in humans. *Am J Trop Med Hyg* 1999; **60**: 831–6.
18. Food and Drug Administration. FDA drug safety communication: FDA approves label changes for antimalarial drug mefloquine hydrochloride due to risk of serious psychiatric and nerve side effects. Updated 29 July 2013. http://http://www.fda.gov/Drugs/DrugSafety/ucm362227.htm
19. Neuberger A, Klement E, Reyes CM, Stamler A. A cohort study of risk factors for malaria among healthcare workers in Equatorial Guinea: stay away from the ground floor. *J Travel Med* 2010; **17**: 339–45.
20. Chen LH, Wilson ME, Davis X, *et al*. Illness in long-term travelers visiting geosentinel clinics. *Emerg Infect Dis* 2009; **15**: 1773–82.
21. Berman JD, Nielsen R, Chulay JD, *et al*. Causal prophylactic efficacy of atovaquone-proguanil (malarone) in a human challenge model. *Trans R Soc Trop Med Hyg* 2001; **95**: 429–32.
22. Sukwa TY, Mulenga M, Chisdaka N, *et al*. A randomized, double-blind, placebo-controlled field trial to determine the efficacy and safety of malarone (atovaquone/proguanil) for the prophylaxis of malaria in Zambia. *Am J Trop Med Hyg* 1999; **60**: 521–5.
23. Leshem E, Meltzer E, Stienlauf S, *et al*. Effectiveness of short prophylactic course of atovaquone-proguanil in travelers to sub-Saharan Africa. *J Travel Med* 2014; **21**: 82–5.
24. Askling HH, Nilsson J, Tegnell A *et al*. Malaria risk in travelers. *Emerg Infect Dis* 2005; **11**: 436–41.
25. Phillips-Howard PA, Radalowicz A, Mitchell J, Bradley DJ. Risk of malaria in British residents returning from malarious areas. *BMJ* 1990; **300**: 499–503.