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Drug-free Holidays: Compliance, Tolerability, and Acceptability of a 3-Day Atovaquone/Proguanil Schedule for Pretravel Malaria Chemoprophylaxis in Australian Travelers

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Background. Poor compliance with chemoprophylaxis is a major contributing factor to the risk of malaria in travelers. Pretravel chemoprophylaxis may improve compliance by enabling "drug-free holidays." The standard treatment dose of atovaquone/proguanil (250 mg/100 mg, 4 tablets/day for 3 days) provides protection against malaria for at least 4 weeks, and could therefore potentially be used for pre-travel chemoprophylaxis. In this study, we assessed the compliance, tolerability, and acceptability of the 3-day atovaquone/proguanil schedule for malarial chemoprophylaxis.

Methods. Two hundred thirty-three participants were recruited from 4 specialized travel medicine clinics in Australia. Adults traveling to malaria-endemic areas with low/medium risk for ≤4 weeks were enrolled and prescribed the 3-day schedule of atovaquone/proguanil, completed at least 1 day before departure. Questionnaires were used to collect data on demographics, travel destination, medication compliance, side effects, and reasons for choosing the 3-day schedule.

Results. Overall, 97.7% of participants complied with the 3-day schedule. Although side effects were reported in 43.3% of the participants, these were well tolerated, and mainly occurred during the first and second days. None of the participants developed malaria. The main reasons for choosing the 3-day schedule over standard chemoprophylaxis options were that it was easier to remember (72.1%), required taking fewer tablets (54.0%), and to help scientific research (54.0%).

Conclusions. The 3-day atovaquone/proguanil schedule had an impressively high compliance rate, and was well tolerated and accepted by travelers. Further studies are required to assess the effectiveness of this schedule for chemoprophylaxis in travelers.

Clinical Trials Registration. ACTRN12616000640404.

Keywords. malaria; chemoprophylaxis; atovaquone; proguanil; travel.

Malaria is an important cause of severe illness and preventable deaths in travelers [1, 2]. An estimated 30 000 cases of travel-related malaria are reported annually [1]. In a study of approximately 7000 returned travelers with fever at GeoSentinel clinics, malaria was the most common diagnosis, accounting for 21% of cases and 33% of fatalities [3]. The mainstay of malaria prevention in travelers is the use of chemoprophylactic medications; a number of effective drugs are available and currently recommended schedules involve taking medications before, during, and after travel to a malaria-endemic area [4]. Atovaquone/proguanil is one of 3 commonly prescribed medications for chemoprophylaxis; the standard adult dosage is 1 tablet (250 mg/100 mg) per day, starting 1–2 days before arriving in a malaria-endemic area, and continuing daily until 7 days after leaving [4]. The other 2 commonly used medications are doxycycline (adult dose 100 mg/day, starting 1–2 days before arriving in a malaria-endemic area, and continuing until 4 weeks after leaving) and mefloquine (adult dose 250 mg/week, starting at least 2 weeks before arriving in a malaria-endemic area, and continuing until 4 weeks afterward) [4].

Although effective medications are available for malaria chemoprophylaxis, their effectiveness is often compromised by poor compliance [5]. Most cases of travel-related malaria are associated with poor compliance or complete failure to take chemoprophylaxis. Studies around the world have found poor compliance among the full spectrum of travelers including tourists [6], backpackers [7], expatriate workers [8, 9], military personnel [10–12], volunteers [13], and those returning to home countries to visit friends and relatives [14]. A study of imported malaria in Australia found that of 246 cases, only 56% took chemoprophylaxis and, of these, only 29% were fully compliant [15]. Failure to take chemoprophylaxis and poor

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compliance have also been associated with an increased risk of severe malaria and malaria-related deaths [16–18].

Improving compliance with malaria chemoprophylaxis could therefore significantly reduce the risk of travel-related malaria and deaths. Poor compliance is at least partly due to the need to take medications for long periods of time. Multiple studies have found that forgetting to take medications was a common problem [19, 20], so compliance could potentially be improved by using simpler medication schedules, such as shorter duration, fewer doses, or schedules that can be completed before travel [5, 21]. In 2007, a group of travel medicine and malaria experts highlighted the need to explore pre-travel malaria chemoprophylaxis regimens, or "drug-free holidays," to improve compliance [5]. However, little progress has been made in the past decade.

Atovaquone/proguanil is highly effective for treating malaria when given at a dose of 1000 mg/400 mg (4 tablets) per day for 3 consecutive days (referred to henceforth as the 3-day schedule). In malaria intervention studies, atovaquone/proguanil has been used to treat any preexisting malaria in the participants. In this setting, studies showed that the 3-day schedule provided protection against malaria for >4 weeks even in highly endemic areas [22, 23]. Studies in volunteers in controlled environments in nonendemic countries have shown similar results [24, 25]. Considering that the elimination half-lives of atovaquone and proguanil are 2–3 days and 14–20 hours, respectively, the lengthy antimalarial activity cannot be explained by simple pharmacokinetics, and is likely to be attributed to the causal prophylactic effect of the drugs on parasites in the liver [5]. A summary of the evidence for atovaquone/proguanil's extended antimalarial activity, and therefore the rationale for its use in chemoprophylaxis, is provided in Supplementary Table 1.

The 3-day schedule's extended antimalarial activity could potentially allow it to be used for prophylaxis, and the short duration of medications (3 days) might improve compliance in travelers. For trips of <4 weeks, travelers could complete the 3-day schedule prior to travel and have a "drug-free holiday" [5]. For longer trips, the 3-day schedule could be repeated every 4 weeks to provide longer protection. For travelers spending >3 days in a malaria-endemic area, the 3-day schedule is also cheaper than the standard daily schedule for atovaquone/proguanil. Other advantages include the ability to manage any side effects before departure (by changing to the standard schedule or different medication), avoiding the problem of not being able to swallow or absorb medications in case of gastrointestinal illness during travel, and removing the need to carry or buy antimalarial medications overseas.

Atovaquone/proguanil is safe and well tolerated as prophylaxis in healthy travelers (1 tablet/day), and as treatment for malaria (4 tablets/day) [26–29]. However, tolerability of the 3-day schedule has not been assessed in the prophylaxis setting, when travelers are usually well and milder side effects might be more be apparent. In this study, we investigated the compliance, tolerability, and acceptability of the 3-day atovaquone/proguanil schedule for pre-travel malaria chemoprophylaxis.

METHODS

Study Design

A single-arm trial was conducted to assess the compliance, tolerability, and acceptability of a 3-day atovaquone/proguanil schedule. Four specialist travel medicine clinics from the Travel Medicine Alliance group in Australia participated: Dr Deb the Travel Doctor, Brisbane; Travel-Bug Vaccination Clinic, Adelaide; Health HQ, Gold Coast; and Travel Medicine Centre Perth.

Study Population

Adults (≥18 years) traveling to malaria-endemic areas in Asia, the Pacific Islands, and South/Central America for ≤4 weeks were eligible. Exclusion criteria included taking medications that interact with atovaquone/proguanil (metoclopramide, rifampicin, tetracyclines, fluvoxamine); pregnancy or planning pregnancy; significant medical conditions (ie, diabetes, heart diseases, asthma, epilepsy, depression, renal or liver impairment, gastrointestinal disorders); and taking long-term antibiotics. Considering that our study was focused on assessing compliance, tolerability, and acceptability (and not effectiveness), travelers to sub-Saharan Africa were excluded from the study because of the higher risk of malaria compared to other regions [1, 30].

Travelers who required malaria prophylaxis were given the options of standard schedules of doxycycline, mefloquine, and atovaquone/proguanil, as well as the 3-day atovaquone/proguanil schedule. Choice of prophylaxis was based on multiple factors including time to departure, duration, and side effects of the medications, daily vs weekly dosing, comorbidities, and personal preference. Pros and cons of options were explained to potential participants, including the "off-label" use of the 3-day schedule for prophylaxis. Cost was also discussed, and travelers or their employers paid for medications regardless of which option was chosen. All travelers who chose the 3-day schedule were enrolled in the study.

Sample Size

Sample size was calculated to identify any differences in the prevalence of adverse reactions with the 3-day schedule in a prophylaxis setting, compared to reported adverse reactions for the standard prophylaxis dose, or the 3-day schedule when used for treatment [26]. Assuming a baseline prevalence of gastrointestinal side effects of up to 15% (ie, diarrhea, nausea, and abdominal pain) [26], 200 participants would be required to provide 90% power at a type I error of 0.05 to detect a 10% difference between groups. Assuming withdrawal or loss to follow-up of 10%, the study aimed for a target sample size of 220.

Informed Consent and Approvals

Information sheets were provided to all participants, and written informed consent was obtained before enrollment. The study was approved by the Australian National University Human Research Ethics Committee (2016/295) and registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616000640404).

Study Intervention and Data Collection

Participants were instructed to take 4 tablets of atovaquone/proguanil (250 mg/100 mg) per day (taken all at once) for 3 consecutive days, with the last dose taken at least 1 day before travel. Participants were encouraged to take each dose with a fatty meal (>24 g), as there is evidence that dietary fat increases the absorption of atovaquone [31] and decreases the likelihood of gastrointestinal side effects.

Participants were asked to contact their clinic if they were unable to tolerate any of the doses, or if side effects were debilitating and they did not wish to continue. For these participants, a doctor or nurse discussed alternative chemoprophylaxis regimens to ensure adequate protection against malaria.

Data were collected using 3 questionnaires, and a memory aid and symptom diary:

1. A travel medicine nurse completed an enrollment questionnaire with each participant. Information was collected on the current trip, previous history of malaria, travel to malaria-endemic areas in the previous 12 months, previous experience with taking antimalarial medications, past medical history, current medications, and allergies.
2. A nurse telephoned the participants and completed a pre-travel questionnaire the day after the 3-day schedule was completed. The nurse confirmed whether the 3-day schedule was taken correctly and documented any side effects during and immediately after the schedule.
3. Within 1 week after return to Australia, a nurse telephoned the participants to complete a posttrip questionnaire, and to collect information on any adverse reactions or diagnosis of malaria during or after travel. Participants were advised to contact the clinic if they were diagnosed with malaria after the post-travel questionnaire.
4. A memory aid and symptom diary was provided to record any symptoms and their intensity for 10 days after starting the 3-day schedule. Symptom severity was defined as mild, moderate, or severe based on the following criteria:
   a. Vomiting: 1–2 episodes in 24 hours; >2 episodes in 24 hours; required intravenous hydration.
   b. Diarrhea: 2–3 loose stools, 4–5 loose stools, or ≥6 loose stools in 24 hours.
   c. Mouth ulcers: easily tolerated, able to eat and drink normally; discomfort, interfered with eating and drinking; incapacitating, great difficulty with eating and drinking.
   d. Other symptoms: easily tolerated, able to continue with normal activities; discomfort, interfered with normal daily activities; incapacitating, prevented normal activities.

Statistical Analysis

All participants who started the 3-day schedule were included in the analysis. Descriptive statistics were used to report the characteristics of the participants. The outcomes (compliance, tolerability, acceptability) were estimated as the proportion of participants who completed the 3-day schedule and reported each outcome over the total number of participants who responded to the pre-travel questionnaire.

Multivariate logistic regression models were built to identify independent predictors of overall side effects, and specific side effects that were reported in >10% of participants. Predictor variables were defined a priori and included gender, age, comorbidities, allergies, taking atovaquone/proguanil with high-fat foods, and prior use of atovaquone/proguanil and/or other antimalarials. Predictor variables were entered using a stepwise forward selection in the regression models. All tests were 2-tailed and a P value <.05 was deemed statistically significant. Analyses were conducted using Stata MP version 14 (StataCorp, College Station, Texas).

RESULTS

Characteristics of the Participants

A total of 233 participants were enrolled in the study from August 2016 to January 2018, of whom 215 (92.3%) completed the enrollment and pre-travel questionnaires and were included in the analysis. After return from their travels, 205 participants were successfully followed up (Figure 1). No participants reported diagnosis of malaria while overseas or upon return.

Median age of participants was 43.8 (interquartile range [IQR], 28.9–57.8) years, and 51.2% were female. Twenty-one participants (9.8%) reported a comorbidity, most commonly asthma (4.7%) and gastrointestinal diseases (3.3%). The majority of the participants reported previous travel to malaria-endemic countries (65.6%) and use of antimalarial medications (50.7%). Sixty-six participants (30.7%) reported previous use of atovaquone/proguanil and only 3 had previously experienced side effects to the medication (ie, nausea in all 3 participants, diarrhea and abdominal pain in 1 participant, and vomiting in another participant). Countries of destination included India, Cambodia, Vietnam, Papua New Guinea, Laos, Myanmar, Indonesia, Thailand, East Timor, Malaysia, Solomon Islands, Brazil, and Ecuador. The main reasons for choosing the 3-day schedule were that it was easier to remember (72.1%), required taking fewer tablets (54.0%), and to help scientific research (54.0%) (Table 1).

Compliance

The 3-day schedule was correctly completed by 210 of 215 participants (97.7%; 95% confidence interval [CI], 94.7%–99.2%).

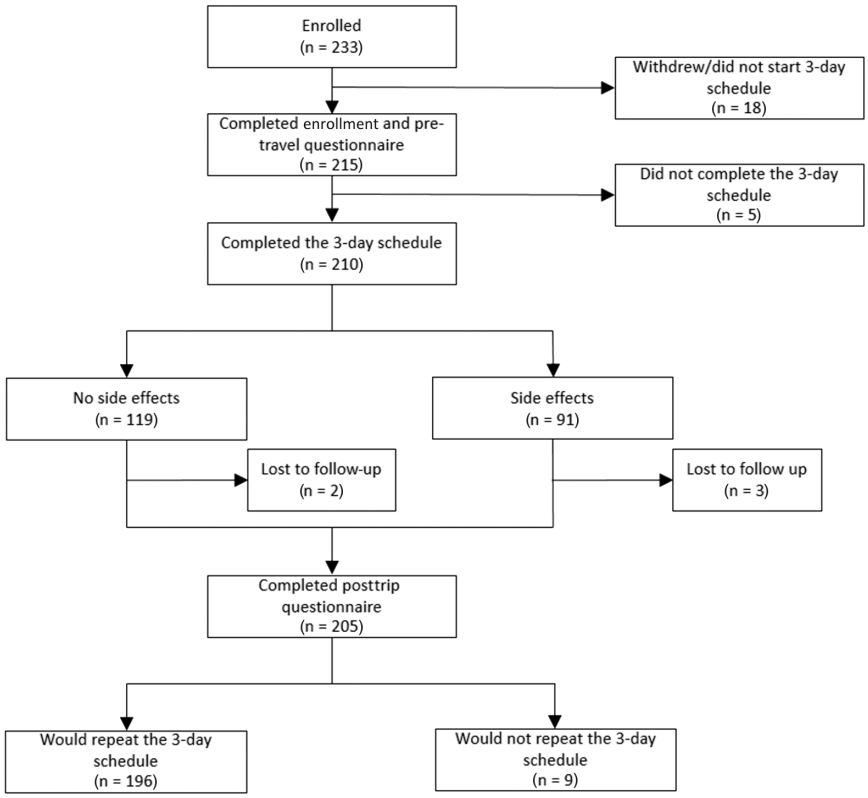

Figure 1. Participant enrollment and follow-up flowchart.

Two did not complete the schedule due to gastrointestinal side effects (diarrhea, nausea, vomiting, or abdominal pain), 2 took the medication every second day or irregularly, and 1 participant discontinued because of an upper respiratory tract infection (Figure 1).

Tolerability

Among those who completed the 3-day schedule, side effects were reported in 91 participants (43.3%) (Figure 1); most commonly nausea (24.8%), diarrhea (17.1%), tiredness (9.0%), headache (5.7%), and dizziness (5.7%). The prevalence of gastrointestinal side effects (33.8%) was higher than for the standard prophylaxis dose (15.9% [26]; $P < .001$), but similar to the 3-day schedule when used for treatment (40.5% [26]; $P = .13$). Side effects were well tolerated and interfered with normal activities in only 3 (1.4%) participants. The majority of the side effects were mild (n = 70 [33.3%]), and only 10% of participants perceived the symptoms as moderate (n = 16 [7.6%]) or severe (n = 5 [2.4%]) (Figure 2 and Supplementary Figure 2). Side effects mainly occurred during the 3 days of the schedule (day 1, 25.7%; day 2, 27.6%; day 3, 19.5%), and rapidly improved thereafter (day 4, 1.9%; day 5, 0.5%). All side effects resolved before departure (Supplementary Table S2 and Supplementary Figure S3). Among those who reported side effects, median duration of symptoms was 2 (IQR, 1–2) days. Three-quarters of participants reported that symptoms lasted for 1 day (n = 44 [48.3%]) or 2 days (n = 25 [27.5%]). Only 20 (22.0%) and 2 participants (2.2%) reported symptoms that lasted for 3 and 4 days, respectively. No participants reported duration of symptoms exceeding 4 days.

Multivariate logistic regression models revealed that females had higher odds of developing overall side effects (odds ratio [OR], 1.79; 95% CI, 1.02–3.14) and nausea (OR, 2.09; 95% CI, 1.07–4.08). Younger participants had higher odds of reporting nausea and the odds decreased by 21% (OR, 0.79; 95% CI, .64–.97) per decade increase in age. No independent predictors were identified for diarrhea (Table 2).

Acceptability

After the trip, 196 participants (95.6%) responded that they would choose to take the 3-day schedule again for future trips. Among the 9 (4.4%) participants who would not use the 3-day schedule again, the main reason was that side effects were unacceptable (n = 7) (Figure 1).

DISCUSSION

Our study provides important data on the compliance, tolerability, and acceptability of the 3-day schedule of atovaquone/proguanil in healthy travelers, and the potential for using this schedule for malaria prophylaxis. The high compliance of (97.7%) is impressive compared to previous studies, which have

Table 1. Participant Characteristics

Characteristic	No. (%)
Demographics	
Female sex	110 (51.2)
Median age, y (IQR) [range]	43.8 (28.9–57.8) [18.3–80.7]
Medical history	
Comorbidities	21 (9.8)
Asthma	10 (4.7)
Gastrointestinal diseases	7 (3.3)
Cardiovascular diseases	3 (1.4)
Depression	3 (1.4)
Allergies to medications	22 (10.2)[a]
Prior exposure to malaria	
Traveled to malaria-endemic country	141 (65.6)
Prior malaria infection	6 (2.8)
Prior use of antimalarial medication	109 (50.7)
Atovaquone/proguanil	66 (30.7)[b]
Doxycycline	50 (23.3)
Proguanil	21 (9.8)
Mefloquine	16 (7.4)
Chloroquine	16 (7.4)
Travel destination	
India	78 (36.3)
Cambodia	34 (15.8)
Vietnam	23 (10.7)
Laos	19 (8.8)
Papua New Guinea	17 (7.9)
Thailand	17 (7.9)
Myanmar	16 (7.4)
Malaysia	12 (5.6)
Indonesia	11 (5.1)
East Timor	10 (4.7)
Solomon Islands	4 (1.9)
Brazil	3 (1.4)
Ecuador	3 (1.4)
Reason for choosing 3-day schedule	
Easier to remember	155 (72.1)
Requires fewer tablets	116 (54.0)
Help scientific research	116 (54.0)
Lower cost	68 (31.6)

Data are presented as No. (%) unless otherwise indicated.

Abbreviation: IQR, interquartile range.

[a]Most common allergies were to penicillins and nonsteroidal anti-inflammatory drugs.

[b]Only 3 participants reported prior side effects.

reported 24%–89% for the standard schedule of atovaquone/proguanil [29, 32], 65%–80% for proguanil [6, 33], 60%–79% for doxycycline [6, 34], and 68%–80% for mefloquine [6, 33, 34]. Considering that poor compliance to chemoprophylaxis is a major contributing factor to travel-related malaria, the 3-day schedule has the potential to significantly reduce malaria in travelers.

Although the 3-day schedule is known to be well tolerated when used to treat malaria, it is difficult to distinguish side effects (eg, nausea, vomiting) from the symptoms of malaria. Our study showed that 4 tablets/day is well tolerated in healthy travelers, and the prevalence of reported side effects were similar to those reported when used for treatment [16]. The majority of side effects were mild, limited to 1–2 days' duration, and completely resolved before departure.

Our study also showed that the 3-day schedule was well accepted by travelers, with >95% indicating that they would choose this option again for future chemoprophylaxis. Travelers readily embraced the idea of "getting the malaria tablets out of the way before departure," or "not having to worry about malaria tablets if I am sick with diarrhea and vomiting." Further studies will be required to directly compare the compliance, acceptability, and tolerability of the 3-day schedule against the standard atovaquone/proguanil prophylaxis schedule and its variations, including twice-weekly dosage [35] or ceasing the medication 1 day after leaving a risk area [36].

The standard prophylaxis dosage of atovaquone/proguanil is expensive compared to other antimalarial medications, and can be prohibitively so for long trips. For a 4-week stay in a risk area, the cost difference between standard daily atovaquone/proguanil (approximately AU$194 for 37 tablets) and the 3-day schedule (approximately AU$63 for 12 tablets) was approximately AU$131 at the clinics where this study was conducted.

The results should be considered in light of the study's limitations. Compliance and acceptability were self-reported and may be subject to participation bias. However, our participants actively sought pre-travel health advice from specialist travel clinics and are generally motivated to take malaria chemoprophylaxis, so it is unlikely for this group to falsely report compliance. Reports on side effects could have been influenced by recall bias, but this was minimized by use of a memory aid and symptom diary. We did not include a control group of travelers taking standard prophylaxis schedules of atovaquone/proguanil or other medications.

No participant was diagnosed with malaria during or after travel, although the study was not designed, nor has the

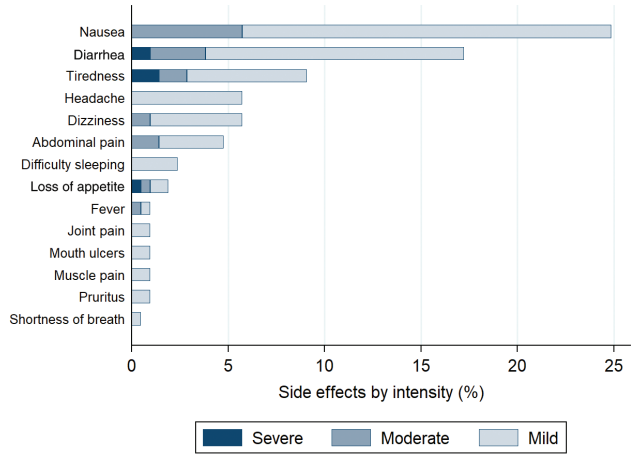

Figure 2. Percentage of participants who reported side effects, stratified by intensity.

Table 2. Univariate and Multivariate Logistic Regression for Predictors of Side Effects

	Overall Side Effects		Nausea		Diarrhea	
Predictor	Univariate Model	Multivariate Model	Univariate Model	Multivariate Model	Univariate Model	Multivariate Model
Gender, female	**1.88 (1.08–3.27)**	**1.79 (1.02–3.14)**	**2.26 (1.18–4.33)**	**2.09 (1.07–4.08)**	1.28 (.62–2.63)	…
Age (per decade increase)	0.88 (.74–1.05)	0.91 (.76–1.08)	**0.78 (.63–.95)**	**0.79 (.64–.97)**	0.98 (.78–1.22)	…
Presence of comorbidities	1.34 (.53–3.39)	…	0.74 (.24–2.32)	…	1.23 (.39–3.94)	1.64 (.56–4.84)
Allergies to medications	1.50 (.61–3.70)	…	1.24 (.46–3.40)	…	1.59 (.54–4.67)	…
Taking atovaquone/proguanil with high-fat foods	1.37 (.77–2.45)	…	1.68 (.88–3.21)	…	0.86 (.39–1.86)	…
Prior use of antimalarial medication	0.90 (.52–1.55)	…	1.17 (.62–2.19)	…	0.73 (.35–1.50)	…
Prior use of atovaquone/proguanil	0.95 (.53–1.71)	…	1.21 (.62–2.36)	1.46 (.73–2.91)	0.68 (.30–1.55)	0.67 (.30–1.53)

Data are presented as odds ratio (95% confidence interval). Boldface data indicate statistically significant results.

statistical power, to assess the effectiveness of the 3-day schedule for prophylaxis. Studies on populations in malaria-endemic areas have provided compelling evidence that the 3-day schedule provides antimalarial activity for up to 5–6 weeks [22–25]. However, further studies, including a larger sample size and higher-risk destinations, will be required to confirm effectiveness in nonimmune travelers.

In an experimental malaria challenge study, heavily infected mosquitoes were allowed to feed on 6 nonimmune volunteers who were given atovaquone/proguanil 1000 mg/400 mg 7 days earlier [37]. One developed parasitemia 21 days postchallenge, but results were questionable because polymerase chain reaction and culture failed to confirm malaria. If the volunteer truly had parasitemia, a single failure after such a severe challenge does not preclude the use of the 3-day schedule for prophylaxis, but signifies that, like all other chemoprophylaxis, it is not 100% effective. The study also showed that chemoprophylaxis failure (in 3 volunteers, including 2 who used other schedules) was associated with poor absorption of atovaquone, and highlights the importance of taking the medications with a large (preferably fatty) meal [37].

Previous discussions on the long-lasting activity of atovaquone/proguanil raised concerns regarding development of drug resistance to atovaquone, because it has a longer half-life and will be present after proguanil has been eliminated [22, 24, 25]. Atovaquone resistance might also be more likely with prolonged or repeated use, for example, repeating the 3-day schedule every 4 weeks in long-term travelers. However, a recent study provided reassuring evidence that atovaquone-resistant parasites are unable to be transmitted by mosquitoes [22]. Also, drug pressure on atovaquone/proguanil created by travelers is unlikely to differ significantly between the standard and 3-day schedules.

In conclusion, our study showed that the 3-day schedule of atovaquone/proguanil is a promising option for malaria prophylaxis, with a very high compliance rate, and was well tolerated and accepted by travelers. Further studies are required to assess effectiveness in nonimmune travelers.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. C. L. L., D. J. M., L. R., and L. M. are employees at privately owned, independent travel medicine clinics that provide advice and medications for malaria prophylaxis. L. F.-K. reports no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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