Do Travelers Really Take Their Mefloquine Malaria Chemoprophylaxis? Estimation of Adherence by an Electronic Pillbox

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Background. Nonadherence to chemoprophylaxis could explain why some travelers get malaria. Adherence is notoriously difficult to assess, and most studies have been conducted using questionnaires. This study aims at assessing continuous adherence more accurately with the help of an electronic pillbox.

Methods. Adult travelers to sub-Saharan Africa had to fill a questionnaire on demographic and travel data, drug intake, and adverse events. They received oral and written information about malaria and mefloquine prophylaxis and a Medication Event Monitoring System (MEMS®, Aardex®, Zug, Switzerland), ie, a bottle closed with a cap containing a microprocessor recording date and time of all openings, filled with the exact number of mefloquine 250 mg tablets (Lariam®, Roche Reinach, Switzerland). The MEMS® was returned with the questionnaire after completion of chemoprophylaxis.

Results. According to the MEMS®, only 26 of 81 travelers (32.1%) took all the doses at the expected date, another 8 (9.9%) did so but starting late with the first dose, and 19 others (23.5%) took all the pills but with intervals of ±1 day from the right date. Another eight (9.9%) took all the pills but in a random way. The remaining 20 travelers (24.7%) missed some doses, mainly after return. Strict adherence as assessed by electronic monitoring was therefore lower than adherence measured by questionnaire (32.1% vs 48% in taking all the tablets on the right day). There was no difference between the two methods when a broader definition of adherence was applied [taking all the tablets on the right day (±1 day); 53/81 (65.4%)], but the MEMS® showed that some answers to the questionnaire were not reliable.

Conclusion. The use of electronic pillboxes confirms the low adherence of travelers to mefloquine chemoprophylaxis in spite of extensive information about the disease and its prevention. Electronic assessment of pill taking, for the first time applied to malaria chemoprophylaxis, gives new insights into the real adherence of travelers.

Regular chemoprophylaxis combined with protective measures against mosquito bites can largely prevent malaria infection and disease.1-4 Imported malaria cases are increasing. Likely explanations are the higher numbers of people traveling to endemic areas and development of drug-resistant malaria. Nonadherence to recommended malaria-preventive schedules might be one potential explanation for the apparent reduced efficacy of antimalarial drugs.4,5

Studies in returning travelers show that most cases of malaria occur in those taking no protective measures and not using any prophylaxis or with the wrong drug or dosage.1,6-8 Adherence is a complex concept mixing understanding of risks, understanding of protective/curative interventions, acceptance of these measures as relevant for oneself, and their application in spite of discomfort.9

Previous studies assessing travelers’ adherence to chemoprophylaxis used questionnaires3,5,10-20

Preliminary results were presented as a poster [Iorio D, Landry P, Darioli R, et al. Electronic monitoring of travelers’ adherence to mefloquine malaria chemoprophylaxis (Abstract C28). Sixth Conference of the International Society of Travel Medicine; 1999 Jun 6–10; Montreal, Canada].

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with the usual limitations for this method of investigation, such as forgetting the precise date and time of drug intake, especially in retrospective questionnaires, or overreporting of the correct regimen in an effort to please the investigators or to hide one’s failure. This has been put into light in the discrepancies between blood levels of drug and questionnaire reporting.\(^2^1\)

A new electronic device able to record date and time of all bottle openings is available to monitor adherence with any treatment more accurately than by questionnaire.\(^2^2\),\(^2^3\) This method has been mainly applied to drugs taken on a daily basis (but no antimalarial drug to our knowledge).\(^2^4\)–\(^2^6\) Data for a weekly dosing regimen such as mefloquine chemoprophylaxis are even fewer.\(^2^7\)

**Objectives**

1. To evaluate travelers’ adherence to malaria chemoprophylaxis with weekly mefloquine 250 mg (Lariam\(^\circledR\), Roche, Basel, Switzerland).
2. To compare adherence as assessed by electronic monitoring with adherence as assessed by standard questionnaire.

**Subjects and Methods**

**Subjects**

Between March and April 1997, every person older than 18 years, traveling to Africa for less than 3 months and consulting our Travel Clinic, Medical Outpatient Clinic, University of Lausanne, Switzerland, was asked to take part in our prospective study. Pregnant women and people with contraindication to mefloquine were excluded. Only one person per couple was included. The protocol was approved by the institutional review board.

**Methods**

Subjects received extensive oral and written information on malaria, its way of transmission, protective measures against mosquitoes, mefloquine chemoprophylaxis, and symptoms of the disease. They were asked to fill an open questionnaire for demographics, medical history, current medical treatment, and travel characteristics before their trip and to complete information on the use of protective measures against exposure, date and time of drug intake, and reasons for missing doses, as well as date, type, and severity of adverse events or any illness related to the journey after they had finished the chemoprophylaxis.

Each one received a Medication Event Monitoring System (MEMS\(^\circledR\), Aardex\(^\circledR\), Zug, Switzerland), ie, a bottle closed with a cap containing a microprocessor recording date and time of all openings (see Figure 1) and filled with the exact number of mefloquine 250 mg tablets required for the journey. To avoid problems with the customs authorities and because of their sensitivity to humidity, tablets were kept in their original blisters. The travelers were made aware of the fact that the MEMS\(^\circledR\) would record all bottle openings and were instructed not to open it except to take the prescribed regimen. The MEMS\(^\circledR\) and the questionnaire were to be returned as soon as the last dose had been taken. A remainder letter or phone call was done to trace nonreturned MEMS\(^\circledR\).

**Malaria Chemoprophylaxis Regimen**

The malaria chemoprophylaxis was prescribed according to the Swiss recommendations of the Swiss Office of Public Health, ie, one tablet of mefloquine 250 mg once a week, starting 1 week before departure and up to 4 weeks after return. Subjects visiting the Travel Clinic less than 1 week before departure were asked to take one tablet on the day of their visit and the second one, 5 days after, before resuming the weekly recommended schedule. Dosing for people more than 90 kg body weight was increased to one and half tablet (375 mg) per week.

**Definition of Adherence**

In this study, complete adherence to prophylaxis was defined as the appropriate taking of all tablets of mefloquine (including 4 weeks after return) at the right date and acceptable adherence as taking of all the tablets at the right date (± 1 day), even if starting less than 7 days before the journey.

**Data Analysis**

MEMS\(^\circledR\) data were analyzed with CSS software (Aardex\(^\circledR\)) and Microsoft\(^\circledR\) Excel 97 SR-1 (Microsoft Corp., Redmond, WA, USA). Data from the questionnaires and the MEMS\(^\circledR\) were analyzed using Epi Info, Version 6.04b software (Centers for Disease Control and Prevention, Atlanta, GA, USA, and World Health Organization, Geneva, Switzerland).

**Results**

From a total of 104 subjects fulfilling the inclusion criteria, 4 refused to enter the study. Of the 100 enrolled, 4 canceled their trip, 1 changed the type
of chemoprophylaxis, 1 had a journey longer than 3 months, 11 did not return their MEMS® and/or questionnaire, and 2 persons had MEMS® with technical failure, leaving 81 subjects for analysis. Of these, 18 (22.2%) had to be recalled to send their material back.

Assessment of Adherence by MEMS®

According to the MEMS®, 61 of 81 (75.3%) travelers took all the tablets, but only 26 of 81 (32.1%) travelers took all the recommended doses at the expected date, as prescribed (Figure 2). Another 8 of 81 (9.9%) travelers did so but started late with the first dose (less than 7 days before the departure), and 19 of 81 (23.5%) took all the tablets but 1 day early or 1 day late on at least one occasion, and 8 (9.9%) took them all but in a random way. Therefore, 20 of 81 (24.7%) missed one or more doses.

Demographics and Travel Characteristics According to the Level of Adherence

Table 1 gives the demographic and travel characteristics of the travelers according to their level of adherence. There was no significant difference in terms of gender, length of travel, time before departure, destination, or purpose of travel. Travelers with an acceptable adherence were slightly older than nonadherent ones (37 years vs 31.5 years, \( p = 0.06 \)), and completely adherent ones even more so (38 years). This latter group was traveling for a shorter period [mean 22.7 days (SD 18.2) vs mean 24.9 days (SD 13.5), \( p = 0.04 \)] when compared to all other travelers. Having taken chemoprophylaxis on a previous trip had no influence on adherence, nor had the destination. Travelers for business or humanitarian purposes were more often adherent, but numbers were small.
Recalls by phone or written notice to recover questionnaires and MEMS® were significantly more common among nonadherent travelers [13 of 28 (46%) nonadherent were recalled vs 5 of 53 (9.4%) adherent ones, (RR 0.33; 95% CI 0.2 – 0.56)]. The theoretical median length of mefloquine intake for the whole group was 8 weeks (range, 7 – 17 weeks).

Twenty-six travelers (32%) reported some minor health problem prior to their travel, and 14 (17%) were taking some medication (seven times antihistaminic or antiasthma). These characteristics had no influence on adherence.

### Adverse Events

The following adverse events were reported by 34 of 81 (42%) travelers: gastrointestinal (nausea, vomiting; n = 16), anxiety or depression (n = 7), dizziness (n = 7), sleeping disorder (n = 4), tiredness (n = 4), headache (n = 4), and other (n = 4). Half of them (16/34) experienced adverse events after one or two tablets already. The adverse events were considered as mild by 9 (27.3% of travelers reporting adverse events), moderate by 11 (33.3%), and severe by 13 (39.4%). Travelers who took all their pills were slightly less likely to have suffered from adverse events [RR 0.48 (0.22 – 1.05), p = 0.06], but there was no statistical difference in the incidence of adverse events between adherent (complete or acceptable) and nonadherent travelers.

### Comparison between MEMS® and Questionnaire

Strict adherence as described above was lower when measured by electronic monitoring (32%) than by questionnaire (48%; Table 2). When a broader definition was used [taking all the pills at the right day (± 1 day)], adherence by electronic monitoring was 65%. When asked if they had taken all the tablets, 62 travelers said that they had, but this was confirmed in only 59 by the MEMS recordings. When asked if they had taken one or more tablets at another date than recommended, 26 travelers admitted it. This was correlated with the MEMS openings in 15 cases. Among the 11 others, 6 stopped completely to take the tablets according to MEMS, leaving 5 cases whose MEMS were opened at the right date but stating in the questionnaire they had not. From the 53 travelers stating that they had not taken any pill on another date than recommended, 10 were found to have done so by MEMS. Therefore, in 21 cases (25.9%), the questionnaire and the MEMS gave discordant results. The questionnaire was not designed to ask for detailed timing of each intake; therefore, it could not provide some of the data given by MEMS in the Table 2.

### Discussion

This is the first study assessing adherence to malaria chemoprophylaxis in travelers, using an electronic recording device.

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**Table 1** Demographic and travel characteristics according to the level of adherence

<table>
<thead>
<tr>
<th>Adherent travelers</th>
<th>Complete adherence, n = 26</th>
<th>Acceptable adherence, n = 27</th>
<th>Nonadherent travelers, n = 28</th>
<th>Total travelers, n = 81</th>
<th>Difference adherent/nonadherent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F, n (%)</td>
<td>14/12 (53.9/46.1)</td>
<td>15/12 (55.6/44.4)</td>
<td>13/15 (46.4/53.6)</td>
<td>42/39 (51.9/48.1)</td>
<td>p = 0.32</td>
</tr>
<tr>
<td>Age* (years)</td>
<td>38 (13.4)</td>
<td>35.9 (11.1)</td>
<td>31.6 (10.0)</td>
<td>35.1 (11.7)</td>
<td>p = 0.06</td>
</tr>
<tr>
<td>Length of stay* (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>22.7 (18.2)</td>
<td>24.2 (12.1)</td>
<td>25.5 (14.8)</td>
<td>24.2 (15.1)</td>
<td>p = 0.23</td>
</tr>
<tr>
<td>Time before travel* (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.4 (14.3)</td>
<td>20.9 (12.1)</td>
<td>22.1 (15.3)</td>
<td>23.1 (14.0)</td>
<td>p = 0.49</td>
</tr>
<tr>
<td>Adverse events, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>East Africa</td>
<td>10 (38.5)</td>
<td>10 (37.0)</td>
<td>14 (50.0)</td>
<td>34 (42.0)</td>
<td>p = 0.20</td>
</tr>
<tr>
<td>West Africa</td>
<td>6</td>
<td>11</td>
<td>10</td>
<td>27</td>
<td>0.94 (0.67–1.32)†</td>
</tr>
<tr>
<td>Central Africa</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>1.02 (0.66–1.58)†</td>
</tr>
<tr>
<td>South Africa</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5</td>
<td>0.60 (0.20–1.76)†</td>
</tr>
<tr>
<td>Main purpose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Business</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>1.60 (1.34–1.90)†</td>
</tr>
<tr>
<td>Humanitarian/social</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>7</td>
<td>1.61 (1.35–1.92)†</td>
</tr>
<tr>
<td>Tourism</td>
<td>15</td>
<td>10</td>
<td>19</td>
<td>44</td>
<td>0.75 (0.55–1.03)†</td>
</tr>
<tr>
<td>Visit friends/family</td>
<td>6</td>
<td>9</td>
<td>9</td>
<td>24</td>
<td>0.94 (0.65–1.34)†</td>
</tr>
</tbody>
</table>

* Continuous variables expressed as means (standard deviation).
† Relative risk (95% confidence intervals).
According to MEMS®, only 26 of 81 travelers (32%) took all their doses strictly following the recommended regimen (ie, starting at the right date and taking it regularly). However, another eight (10%) did so with a delay in starting it, and 19 (23%) complied with chemoprophylaxis according to a +1 day schedule, which we judge to be an acceptable level of adherence. Indeed, for the latter group, and due to the long half-life of mefloquine (25 days) and its kinetics, we assume that taking the tablets 1 day before or after the scheduled day would hardly modify the blood level and hence protection. Starting mefloquine chemoprophylaxis only 1 week before a potential exposure as recommended in the guidelines could leave travelers with nonprotective blood levels in the first weeks of their trip. This could have been a particular concern for the travelers who started to take their pill later than recommended, even if they took them all and regularly. The real protection conferred by taking all the tablets but in a random way [8/81 travelers (10%)] is impossible to assess without monitoring mefloquine blood levels.

Previous studies aiming at assessing travelers’ adherence to chemoprophylaxis with weekly mefloquine using oral or written retrospective questionnaires gave adherence rates between 21 and 98%. The interpretation of such a wide range of results is difficult. Questionnaire assessment has been shown to overestimate adherence when compared to pill count or to drug blood levels. One important reason for this is that the travelers do not remember when they take their tablets exactly. Also, they fear to displease the investigator or to appear as unreliable and therefore give what they think is an acceptable answer. Using an electronic device, recording openings should prove more accurate. In our study, the level of adherence was similar by both methods, but the comparison of both methods showed that in about 25%, the answers to questions of timing by questionnaire were unreliable. Eighteen travelers had to be recalled at least once to send the MEMS® and the questionnaire back after their trip, and they were more likely to be nonadherent. We presume that at least some of them filled their questionnaire after return only and not during their trip, which could explain part of the discordant results between both methods. We doubt that asking for more precise details about timing of each intake in the questionnaire could have given reliable information.

Both the methods are thought to have a reminding effect, the impact of which is not known. Our study was not designed to measure this impact, which could well have been of some importance as travelers were assessed by both methods at the same time. Therefore, our results like other studies probably overestimate adherence, but the MEMS method gives some insights into the real behavior of travelers.

Nonadherence in taking any medication for prevention of hypothetical risks is higher than in taking medication against symptomatic diseases. This is probably even more so when on holiday. Adverse events are a known factor for poor adherence. In this study, about one-quarter of travelers did not take all the tablets, mostly after return, and the main reasons given were adverse events and forgetfulness, but there was no statistical significance between adherent and nonadherent travelers. Nonadherence was linked to younger age and travel of longer duration. This has also been demonstrated in other studies. Also, people traveling for business or short-term humanitarian reasons were more likely to be adherent than tourists, but the relative small number of participants did not allow for a complete study of the factors and characteristics leading to adherence or nonadherence.

A limitation of our study is the absence of another group assessed by questionnaire only, which could have given some more information regarding comparative adherence between the two methods and about the reminding effect. Also, the cut blisters of

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison between MEMS® and questionnaire</th>
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<tbody>
<tr>
<td></td>
<td>MEMS®</td>
</tr>
<tr>
<td>Full adherence (all the tablets at the right day)</td>
<td>26/81 (32.1%)</td>
</tr>
<tr>
<td>Full adherence but started late</td>
<td>8/81 (9.9%)</td>
</tr>
<tr>
<td>All the tablets at the right day (± 1)</td>
<td>45/81 (55.6%)</td>
</tr>
<tr>
<td>Took all the tablets but at various intervals</td>
<td>8/81 (9.9%)</td>
</tr>
<tr>
<td>All tablets (any time)</td>
<td>61/81 (75.3%)</td>
</tr>
<tr>
<td>Did not take all the tablets</td>
<td>20/81 (24.7%)</td>
</tr>
<tr>
<td>Missed one or more doses but resumed taking</td>
<td>3/81 (3.7%)</td>
</tr>
<tr>
<td>Stopped completely during the trip</td>
<td>3/81 (3.7%)</td>
</tr>
<tr>
<td>Stopped completely after the trip</td>
<td>14/81 (17.3%)</td>
</tr>
<tr>
<td>Adverse events</td>
<td>No data</td>
</tr>
</tbody>
</table>

MEMS®, Medication Event Monitoring System.
mefloquine in the MEMS® bottles could have lacked the reminder effect of a standard packet of tablets as to whether medication was taken or not. Studies assessing compliance of weekly drug intake with a MEMS® are few. A trial comparing weekly versus daily fluoxetine gave 87.8% adherence in the weekly group versus 79.0% (p = 0.006) in the daily group.25 Using questionnaires, adherence with weekly mefloquine was 94.5% compared to 79.8% with daily chloroquine/proguanil.26

A study of adherence to daily atovaquone proguanil HCL (Malarone®, GSK, Muenchenbuchsee, Switzerland; was not yet marketed at the time of our study) or doxycycline (rarely given for destinations in Africa in our Travel Clinic) by MEMS® could prove interesting.

Conclusion

The use of electronic pillboxes shows that adherence to mefloquine chemoprophylaxis is too low in spite of a good oral and written information about the disease and its prevention. Most of the travelers who stopped the chemoprophylaxis did so after return, and they tended to be younger and traveling for longer periods than those who were more adherent to recommendations. The electronic pillboxes gave new insights in the way travelers were taking their pills, showing that very few did follow the recommendations strictly. It also showed that questionnaire answers about timing of intake were unreliable.

A cheap, well-tolerated, simple, and short-course chemoprophylaxis regimen is desirable to increase adherence in travelers, but unless it is a short-course regimen preferably before departure only, it is likely that adherence will remain unsatisfactory. In the mean time, travelers should be strongly advised to consult medical facilities in case of fever, especially if they stopped their chemoprophylaxis.

Acknowledgment

MEMS® boxes and Lariam® were provided by Roche Company.

Declaration of Interests

The authors state that they have no conflicts of interest.

References