SERIOUS ADVERSE EVENTS OF MEFLOQUINE IN RELATION TO BLOOD LEVEL AND GENDER

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Abstract. Mefloquine is widely used for prophylaxis in areas with chloroquine-resistant falciparum malaria. As the use of mefloquine has increased, so have the reports on its adverse effects. We sought to evaluate the possible association between serum levels of mefloquine and serious side effects caused by this drug by means of a case-control design study. The study population included 17 patients who presented to emergency rooms or travel clinics with symptoms suggesting serious adverse effects of mefloquine and 28 controls (healthy people, still taking mefloquine after travel). The mean age of the patients and the controls was 31.5 ± 11.6 years and 34 ± 12.2 years, respectively. The percentage of women among the patients was higher than in the control population (76% versus 40%, respectively; \( P = 0.03 \)). Most of the complaints were related to the central nervous system (13 of 17); 5 patients interrupted their trip and 2 others were hospitalized. No difference in the level of mefloquine in the blood was found between the patients and the control groups. Also, no significant difference was found between mefloquine levels in the blood of men and women. These results suggest that blood levels of mefloquine do not correlate with its severe adverse events. Women tended to be more susceptible than men, despite having similar blood levels of the drug.

INTRODUCTION

Mefloquine has gained popularity for malaria prophylaxis in the areas of widespread chloroquine-resistant \textit{Plasmodium falciparum} malaria. Mefloquine is thus recommended as the drug of choice by the health authorities in the United States, United Kingdom, and Israel, as well as in other countries, for travelers going to areas with chloroquine-resistant \textit{P. falciparum} malaria. An additional advantage of mefloquine over other available antimalaria drugs that are taken daily is its long half-life of \( \sim 21 \text{ days} \). This feature permits longer between-dose intervals and thus may increase patient compliance with the drug regimen. The long half-life has promoted the drug’s initial recommendation to take the drug once in 2 weeks. However, observations among U.S. Peace Corps volunteers in Africa showed that with this dose interval, some people experienced suboptimal drug levels \(^5\) and hence contracted malaria. Consequently, the recommendations were changed to a once-weekly dosage of 250 mg for adults.

As the use of mefloquine increased, it was followed by reports on its adverse effects.\(^3,4\) The most commonly reported adverse effects relate to gastrointestinal problems,\(^3\) but consumers were much more concerned about the central nervous system adverse effects.\(^5\) These included sleep disturbances, dizziness, induction of epilepsy, and depression in susceptible people.\(^10,11\)

The aim of this study was to evaluate the possible association between serum levels of mefloquine and serious side effects caused by this drug by means of a case-control design study.

PATIENTS AND METHODS

During a period of 18 months starting from June 1997, 45 patients approached our 2 travel medicine clinics after they had received mefloquine therapy. Of these, 17 came because of serious adverse effects of mefloquine and 28 for other reasons, such as completion of previous vaccinations, or posttravel check-up without any specific complaints. The latter group was designated as the control group.

Grading of adverse events was made in accordance with Barrett and others\(^12\) as follows: Grade 1, relatively trivial symptoms; 2, bad enough to interfere with daily activities; 3, requiring medical advice; and 4, requiring hospitalization. All patients included in our case study group were assigned to Grades 3 or 4.

In addition to blood samples collection, both patients and controls were questioned about the total number of mefloquine tablets consumed, the date of intake of the last tablet, concomitant consumption of other medications, and possible side effects. Clinical assessment ruled out other reasons for the patients’ complaints. The study was approved by the ethical committees of the 2 participating hospitals. Blood was drawn after informed consent was obtained.

Mefloquine serum level measurements were performed by the laboratory of Clinical Pharmacology and Toxicology, Sheba Medical Center, Tel-Hashomer, Israel. Serum mefloquine concentration was measured by high-performance liquid chromatography by use of a modification of the method of Ward and others.\(^13\)

Briefly, 0.5 mL serum and 0.5 mL NaOH 0.1 N were added to 6 mL chloroform containing internal standard (200 ng/mL chloroquine) and were incubated for 30 min. The organic phase was evaporated in a speed-vac instrument (Savant Instruments, Farmingdale, NY). The dry pellet was reconstituted with 125 \( \mu \text{L} \) mobile phase, and 50 \( \mu \text{L} \) were injected into an HP 1050 high-performance liquid chromatography instrument (Hewlett Packard, Palo Alto, CA) at ambient temperature. Separation was carried out on a Lichrospher 125- by 4-mm RP 18 column (Merck, Darmstadt, Germany) at a flow of 1 mL/min. The mobile phase consisted of acetonitrile, methanol, and water (44:19:37) containing \( 5 \times 10^3 \) mol/L heptanesulfonic acid. The system was equipped with a variable wavelength detector set at 222 nm.

For statistical analysis, a regression analysis model, for which we used S-Plus software, was used to compare serum concentrations of mefloquine with the occurrence of adverse events.
levels of mefloquine between patients and controls and to determine the effect of mefloquine levels as a risk factor for serious adverse effects. Because different subjects participating in the study presented on different days after the last dose of mefloquine, their serum levels could not be combined as a group. Therefore, mefloquine serum levels were described according to the time elapsed after intake of the last dose.

**RESULTS**

The study group included 17 patients and 28 controls. The mean age of the patients was 31.5 ± 11.6 years, and the mean age of the controls was 34 ± 12.2 years. Although most of the patients were women (76%), the majority of the group designated as controls were men (60%) (P = 0.03; Fisher exact test). The male-to-female ratio among the control subjects seems to be representative of our travelers’ population. Indeed, during the 18-month period of this study ~5,000 travelers attended our clinics before traveling, of whom 60% were men. Thus, the odds ratio for developing serious adverse events after mefloquine administration was 5.02 higher in women as compared with men (95% confidence interval [CI], 1.3–19.4).

The most common side effects were related to central nervous system toxicity (n = 13); the others were gastrointestinal toxicity (n = 3) and cardiac toxicity (n = 1). Among the central nervous system effects, dizziness (n = 6), anxiety, and restlessness (n = 4 for each) were the most common. All the patients were previously healthy, without any known risk factors for mefloquine adverse effects, except Patient 11, who had a history of anxiety.

Five of the travelers had to terminate their trip prematurely and be evacuated home. Patient 2 needed a physician’s escort from Brazil to Israel. Three travelers needed hospitalization, 2 for severe dizziness, whereas the third had recurrent visits to the emergency department for palpitations and tachycardia. Three patients experienced severe and prolonged psychiatric reactions. Two of them had traveled abroad before, without any complications. In 2 travelers, the symptoms started after a single dose of mefloquine (Table 1) and continued despite cessation of the drug. All subjects needed psychiatric intervention and prolonged anxiolytic treatment. It is of interest that all these severe and prolonged reactions occurred among men.

Figure 1 presents a comparison of the blood levels between the 2 study groups by time after drug administration. No significant differences were noticed between people with serious adverse events and those who did not have any complaints. Calculating the odds ratio (adjusted for the day after drug administration) while categorizing the patients into 2 groups; subjects with high serum levels (≥500 ng/mL) and those with low serum levels (<500 ng/mL) did not demonstrate any significant difference (odds ratio = 0.6, 95% CI, 0.1–3.5, P = 0.6).

We also analyzed a subgroup of patients and controls who presented 6–10 days after the last dose (trough level) who had taken at least 4 doses of the drug (close to steady state). Average serum level among patients (n = 6) was 904 ± 292 ng/mL, which was not significantly different from controls.

**Table 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Adverse effects</th>
<th>No. of tablets</th>
<th>Impact of adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37/F</td>
<td>Severe dizziness, nausea</td>
<td>5</td>
<td>Hospitalization</td>
</tr>
<tr>
<td>2</td>
<td>24/M</td>
<td>Prolonged, severe anxiety</td>
<td>1</td>
<td>Trip interrupted</td>
</tr>
<tr>
<td>3</td>
<td>53/F</td>
<td>Palpitations, anorexia, insomnia, mood change</td>
<td>2</td>
<td>Trip interrupted</td>
</tr>
<tr>
<td>4</td>
<td>50/F</td>
<td>Restlessness, abdominal pain</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>21/F</td>
<td>Palpitations</td>
<td>2</td>
<td>Emergency room visit</td>
</tr>
<tr>
<td>6</td>
<td>27/F</td>
<td>Severe headache, dizziness</td>
<td>8</td>
<td>Trip interrupted</td>
</tr>
<tr>
<td>7</td>
<td>24/F</td>
<td>Abdominal pain, vomiting, diarrhea</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>21/F</td>
<td>Restlessness, dizziness, nausea</td>
<td>6</td>
<td>Hospitalized in Kenya</td>
</tr>
<tr>
<td>9</td>
<td>49/M</td>
<td>Sleep disturbances, low-grade fever, sweats</td>
<td>3</td>
<td>Emergency room visit</td>
</tr>
<tr>
<td>10</td>
<td>28/F</td>
<td>Nausea, dizziness</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>25/F</td>
<td>Dizziness, headache, anxiety</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>22/F</td>
<td>Restlessness, nausea, choking</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>29/M</td>
<td>Anxiety, restlessness, phobia</td>
<td>7</td>
<td>Trip interrupted</td>
</tr>
<tr>
<td>14</td>
<td>26/F</td>
<td>Dizziness, nausea, lack of concentration</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>23/F</td>
<td>Mood changes: hyperactivity-depression, nightmares, hallucinations</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>29/M</td>
<td>Severe anxiety state</td>
<td>1</td>
<td>Trip interrupted</td>
</tr>
<tr>
<td>17</td>
<td>52/F</td>
<td>Nausea, abdominal pain, fever</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Plotting our patients’ blood levels while the patients were symptomatic shows no difference between the patients and controls (Figure 1). Further analysis of a small subgroup of patients and controls who were at their trough levels showed no significant different in the blood levels. Similar findings were found in another study in patients with nonserious adverse events.14

Although most of the affected was composed of men (60%, which reflects the population of travelers to tropical countries), most of the affected were women (76%). Because our study group is composed of people who came voluntarily for consultation, this overrepresentation of women among the patient group can either be due to a selection bias of people who came for consultation after their trip or to a genuine higher risk for women to develop side effects to mefloquine. Other researchers have also noted a higher rate of side effects among women. Phillips and Kass17 noted that women consistently reported more adverse effects than men and were more likely to discontinue mefloquine because of adverse effects. These authors also pointed out that overreporting by women is unlikely to explain why they experienced the most severe adverse effects. Similarly, in a large German study, women taking mefloquine reported significantly more side effects than men.18 In the large comparative study of Barrett and others,12 most of the patients with disabling neuropsychiatric adverse events due to mefloquine were women.

Sex-related differences in drug metabolism have been described for other drugs.19,20 Such differences might lead to higher blood levels of mefloquine in women and thus explain their higher rate of side effects. One may also hypothesize that, because of a relatively lower body weight, women may have higher blood levels of mefloquine and thus more adverse effects. However, our study did not show a difference in blood levels between men and women, and thus we could not support these theories. An alternative explanation could be that the higher cerebral flow in women might favor the distribution of the drug to the brain,21 explaining the fact that most of their complaints are due to central nervous system involvement.

Most previous studies included patients with minor adverse events. In contrast, the present study focused exclusively on patients who experienced severe symptoms that necessitated medical attention. Some of the patients had to terminate their trip prematurely; had to be referred to the emergency department; or had to be hospitalized. Our study suggests that blood levels of mefloquine do not correlate with its severe adverse effects. Women tended to complain more of mefloquine adverse effects than men, despite having similar blood levels of the drug. Most of the patients had their complaints within the first 3 doses. Therefore, starting prophylaxis 3 weeks before traveling may be considered to identify people susceptible to adverse events related to this drug before their trip.

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