Neurological, cardiovascular and metabolic effects of mefloquine in healthy volunteers: a double-blind, placebo-controlled trial

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1 To assess neurological, cardiovascular, metabolic and other side-effects of mefloquine given in conventional prophylactic dose to healthy volunteers, a double-blind, randomized, placebo-controlled trial was conducted. In addition, the identity of the active drug was concealed until the end of the trial.

2 A total of 106 healthy adults were recruited, of whom 95 (mean age 24 years; 45% males) completed the full study protocol.

3 Subjects had a baseline assessment, received placebo as first dose, were randomized to mefloquine 250 mg or placebo weekly for 4 weeks starting a week later, and were reassessed after the 2nd and 4th active/placebo doses. Subjects kept a daily symptom diary from 2 weeks before until 2 weeks after the dosing period.

4 Plasma mefloquine assay suggested compliance in all 46 subjects allocated active treatment (week 5 mean ± s.d.; 2.35 ± 0.94 μmol l⁻¹). Mefloquine did not alter calcium homoeostasis but produced a mean 0.5 mmol l⁻¹ fall in serum glucose over the study period (P<0.001) and relative hyperinsulinaemia. Symbol digit modalities, and digit forwards and backwards test scores, were similar in active and placebo groups across the three assessments, as were lying/standing blood pressure and high-tone hearing loss. Electrocardiographic QTc interval prolongation and diarrhoea were mild but transient side-effects of mefloquine (P<0.01). Neurological symptoms were comparable in the two groups throughout the study. There was no evidence of drug toxicity in 11 subjects who withdrew.

5 Mefloquine prophylaxis does not appear to produce low-grade but debilitating neurological symptoms or to alter the results of sensitive tests of cerebral function. However, there may be situations in which mefloquine might contribute to hypoglycaemia and cardiac dysrhythmias.

Keywords mefloquine side-effects neurological function glucose insulin

Introduction
Mefloquine can be used as prophylaxis or treatment for malaria and covers most multi-drug resistant strains of Plasmodium falciparum. Although large-scale studies have affirmed its relative safety and efficacy as a prophylactic agent [1–3], serious side-effects including isolated cutaneous [4–6] and marrow toxicity [7, 8] have been reported. Severe neuropsychiatric reactions are more common [9], with an estimated frequency of 1 in 10,000 to 14,000 prophylactic courses [10, 11]. Review of 59 such reactions has revealed that a large proportion of patients had a past history of neurological or psychiatric diseases such as epilepsy and manic-depressive illness [12]. Milder and more common neurological effects including dizziness, vertigo, paraesthesiae, depression, fatigue, insomnia, and poor concentration and memory can
occur soon after ingestion of a single mefloquine dose and persist for weeks afterwards [1, 13–17]. However, physician warnings of neuropsychiatric reactions, and the stresses and stimulation of travel, might produce such symptoms in susceptible individuals. A review of 109 trials involving healthy subjects has revealed an adverse event frequency on placebo of 19% in single and 28% in multiple dose studies [18]. Headache, drowsiness, poor concentration and aesthenia are reported commonly in young volunteers.

To investigate whether mild but debilitating neurological symptoms occur during a conventional prophylactic mefloquine regimen and, if so, whether metabolic disturbances might contribute, we conducted a double-blind, randomized placebo-controlled study in healthy volunteers who were unaware of the identity of the drug under evaluation until the end of the trial.

Methods

Subjects

Subjects were healthy adult staff and students at teaching hospitals in Perth, Western Australia. All completed a standard medical questionnaire. Those with a past history of psychiatric conditions, or neurological, cardiac, hepatic or renal disease were excluded, as were pregnant or breast-feeding females and those with a known allergy to, or taking medication known to interact with, quinoline drugs. None of the subjects had taken mefloquine in the 3 months before study.

Methods

The study protocol was approved by the University of Western Australia Human Rights Committee. Witnessed informed consent was obtained after full verbal and written explanations of procedures, including advice that the identity of the active formulation would be concealed until the end of the study unless an adverse event occurred. Subjects were asked to reattend for assessment 1 day after the third and fifth (last) tablets had been taken, at a time when plasma mefloquine concentrations would be expected to be close to maximal post-dose. At these visits, diaries were reinspected and compliance checked by questioning and tablet count. Blood sampling and all other tests were repeated. Each subject was asked to maintain the diary until 2 weeks after the last assessment when it was collected. Assay of mefloquine and metabolite was by high performance liquid chromatography [21]. Serum glucose, albumin, phosphate and magnesium concentrations were analysed using Chem-1 methods (Bayer Diagnostics, Tarrytown, NY). Serum ionised calcium was determined using an ICA 2 analyser (Radiometer, Copenhagen) and corrected to pH 7.40. Serum insulin was measured immunoenzymetrically (Tosoh, Tokyo, Japan).

Data analysis

To detect at least a 10% difference between the two groups for both SDMT [19] and digit span forwards test [20] using a 0.05 significance level at 80% power, a minimum sample size of 47 in each group was required. For diary data, a positive symptom was taken as a rating \( \geq 1 \) for at least 1 day during a given week. Major symptoms were those rated \( \geq 5 \) on any one day of the week. To assess the effect of mefloquine on symptoms, the proportions of subjects in whom a symptom rating worsened during the first week after active drug or unsupervised placebo were calculated using the rating from the week following the initial supervised and universal placebo as baseline. The relative risk was taken as the ratio of the proportion worsening after mefloquine to that after unsupervised placebo. This analysis was repeated for the week after the last dose, again using the rating after supervised placebo as baseline. For psychometric tests, retest gain (the percentage improvement or deterioration in scores relative to baseline) at the second and third assessments was calculated by the formula:

\[
\text{score at follow-up-score at initial assessment} \times 100\text{score at initial assessment}
\]

Serum insulin concentrations were log-transformed before analysis. Statistical analysis was by parametric methods using SPSS for Windows (SPSS Inc., Chicago, USA). Two-sample comparisons were by Student’s t-test and multiple comparisons by analysis of variance. Pearson’s correlation co-efficient was used to assess associations between variables.

Results

Subjects

Of 106 randomized volunteers, 95 (90%) completed all study procedures. Forty-six of these received mefloquine and 49 placebo. Age and sex distributions of those on mefloquine (23.5 ± 6.3 years, 51% males) were not significantly different from those on placebo (24.6 ± 7.8 years, 39% males; P > 0.1), and body weights were similar (65.3 ± 11.2 and 66.7 ± 10.6 kg respectively, P = 0.26). Eight subjects withdrew after initial assessment and three after the second. Follow-up of these individuals revealed no toxicity in those allocated mefloquine. Reasons for withdrawal were a lack of time to devote to study procedures, including completion of diaries, in 10 individuals and accidental injury in a volunteer receiving placebo.

Compliance and plasma mefloquine concentrations

Compliance appeared full on direct questioning and tablet count at follow-up visits though several volunteers reported taking tablets a day or two late between assessments. Plasma mefloquine and its carboxy metabolite were measurable at both the second and third assessments in all allocated active formulation. After two doses, plasma mefloquine ranged from 0.25 to 2.82 (mean 1.52) μmol l⁻¹ and carboxy-metabolite concentrations were from 0.25 to 6.24 (mean 2.35) μmol l⁻¹; the average metabolite:drug ratio was 2.0. After the last dose, the equivalent figures were 0.94 to 5.37 (mean 2.35) μmol l⁻¹ and 1.4 to 9.5 (mean 5.3) μmol l⁻¹ respectively, with an average carboxy-metabolite: mefloquine ratio of 2.6.

Symptom reporting

The most common symptom during the run-in week and week after universal placebo was headache. Approximately half the total sample experienced at least mild headache (rating ≥1) on one or more days during this period (see Table 1). This proportion remained relatively constant during the ensuing six weeks. There was no increase in the relative risk of this symptom occurring after the first and last mefloquine dose (see Table 1). The number of subjects experiencing major headache (rating ≥5) remained low (1 or 2 participants) and comparable between the two groups throughout.

A similar pattern was seen for the listed diary symptoms lethargy, cough and the other less frequently positive (<10%) non-gastrointestinal complaints skin rash, itch, dizziness, hearing loss, tinnitus, memory loss, visual disturbance, insomnia and vivid dreams. In the first week after mefloquine administration, mild abdominal pain and nausea increased but this trend did not reach statistical significance (see Table 1). However, diarrhoea worsened significantly after mefloquine (see Table 1; P < 0.01), an effect which was transient and not associated with an increase in its rating as a major symptom (see Figure 1).

Biochemical variables

Serum ionised calcium concentrations remained stable over the study period (mean ± s.d.; 1.24 ± 0.03 mmol l⁻¹ at first and final assessment for subjects on active and placebo treatment respectively), as did serum magnesium and phosphate (P > 0.5). The mean serum albumin fell approximately 1 g l⁻¹ in both groups (P < 0.004 baseline vs final assessment). A progressive fall in serum glucose over the three assessments was observed in those on active formulation (5.0 ± 0.7 vs 4.5 ± 0.8 mmol l⁻¹ at baseline and final assessments respectively; P = 0.0005). This fall was proportionately greater than that of serum albumin and was accompanied by a significant increase in serum insulin (geometric mean [ ± 1 s.d. range]; 10.6 [5.7–19.8] vs 15.7 [2.7–31.9] μIU l⁻¹ respectively; P = 0.01; see Figure 2). No significant changes in serum glucose or insulin were seen in the placebo group (P > 0.2; see Figure 2). Plasma mefloquine concentrations at the final assessment and the change in serum insulin over the 5 weeks of the study did not correlate significantly (r = 0.203; P = 0.09). The lowest serum glucose (2.5 mmol l⁻¹) occurred in asymptomatic individuals from both groups at the second assessment.

Psychometric testing

Subjects in the two groups had comparable mean baseline scores for all three tests (P > 0.14). There was a significant improvement in retest gain in SDMT and digit span backwards scores during the study in the placebo group (P < 0.01). In those allocated mefloquine, significant learning was evident only in the case of SDMT score (P < 0.001). However, retest gain at the third assessment was not significantly different between the two groups for DMST (P = 0.25), digit forwards (P = 0.16) and digit backwards (P = 0.08) tests (see Figures 3 and 4).

Audiometric, blood pressure and electrocardiographic changes

There was no significant hearing loss at 6 kHz in either the active or placebo groups over the three assessments (P > 0.2; see Table 2). Systolic and erect blood pressure also showed no changes during the study (P > 0.2; see
Table 1 Percentage of subjects reporting symptoms of at least mild severity (rating ≥1) in the week after initial universal placebo (baseline). The relative risk and (95% confidence intervals) of each symptom worsening from baseline after active (n = 46) compared with placebo (n = 49) treatment is shown for both first and last doses. Other symptoms occurred in <10% of subjects in both groups.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Week after placebo dose (all subjects)</th>
<th>Relative risk of symptom worsening in mefloquine compared with placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mefloquine</td>
<td>Placebo</td>
</tr>
<tr>
<td>Headache</td>
<td>45%</td>
<td>60%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>49%</td>
<td>43%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26%</td>
<td>20%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>27%</td>
<td>16%</td>
</tr>
<tr>
<td>Cough</td>
<td>27%</td>
<td>14%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13%</td>
<td>17%</td>
</tr>
</tbody>
</table>

* P < 0.01
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Time of study

Serum glucose (mmol l\(^{-1}\))

Serum insulin (\(\mu l^{-1}\))

Week 1

Week 5

Week 1

Week 5

**\(P<0.001\)

*\(P<0.01\)

Figure 2 Serum glucose (mean ± s.d.; left panel) and insulin (geometric mean ± s.d.; right panel) in patients allocated mefloquine (\(\text{L}--\text{L}\)) before (week 1) and at the end of (week 5) four weekly doses of 250 mg, and in the placebo group (\(\text{S}--\text{S}\)) at the same times. There was a significant fall in serum glucose (**\(P<0.001\)) and rise in insulin (*\(P<0.01\)) in the mefloquine group.

Figure 3 Retest gain as a percentage of baseline for Digit Symbol Modalities Test score in subjects receiving mefloquine (\(\text{L}--\text{L}\)) or placebo (\(\text{S}--\text{S}\)) over four weeks.

Figure 4 Retest gain as a percentage of baseline for digit span forwards (top panel) and digit span backwards (bottom panel) test scores in subjects receiving mefloquine (\(\text{L}--\text{L}\)) or placebo (\(\text{S}--\text{S}\)) over four weeks.

and a possible bias against mefloquine, might have been expected in this situation. Given our results and those of other trials involving young volunteers [18], there was little evidence of such an effect in the present study.

In other large-scale studies, nausea, dizziness and headaches were reported by between 6 and 12% of European travellers on mefloquine [2], while strange dreams, insomnia and nausea were present in 10 to 25% of U.S. Peace Corps volunteers on long-term prophylaxis [3]. These data suggest that different side-effect profiles reflect discrepancies between demographic characteristics of study populations, as well as itinerary, comedication rates and even pre-travel advice and warnings. Nevertheless, gastrointestinal side-effects seem

to be the most consistent in all studies to date. Our data do not support an increase in mild and debilitating neurological symptoms during mefloquine prophylaxis. Consistent with known frequency of serious neuropsychiatric reactions from large scale trials [10, 11], none was observed in our relatively small sample.

The change in serum albumin over the study period in both groups was difficult to explain but of limited biological significance. The stability of serum ionised calcium and magnesium during weekly mefloquine dosing argues against disturbances in mineral homeostasis contributing to even mild neurological effects. The fall in plasma glucose seen in subjects taking mefloquine was proportionately greater than that in serum albumin and appeared to result from relative hyperinsulinaemia. Mefloquine is related chemically to the cinchona alkaloids. It is, therefore, possible that it has a quinine-like effect on the pancreatic beta-cell [24] even though the correlation between plasma drug concentrations and changes in serum insulin from baseline did not achieve statistical significance.

There are limited data on the effect of mefloquine on glucose homeostasis. In a study involving seven healthy volunteers, plasma glucose and insulin remained close to baseline during the 6 h after a single dose [25], a period which is much shorter than the time at which maximal plasma mefloquine concentrations are usually reached [23]. Although our subjects were not studied in a fasting or timed post-prandial state, most attended several hours after eating. Serum glucose and insulin concentrations were largely within post-absorptive ranges and suggest that peak mefloquine concentrations on a background of regular dosing may result in hyperinsulinaemia. This effect, when coupled with other factors such as prolonged fasting or ethanol ingestion, could produce hypoglycaemic symptoms and even serious consequences of neuroglycopena such as convulsions [12]. Recent reports of mefloquine-associated hypoglycaemia in a cachectic patient with AIDS [26] and in an individual after alcohol consumption [27] support this hypothesis.

Psychometric testing revealed no significant effects of mefloquine on neurological performance. This reflects both the infrequent reporting of impairment of memory, concentration and motor function by those volunteers on active formulation and previous data from young subjects on long-term mefloquine [3] in whom less than 2% considered that the drug interfered with daily activities. Median values for 6 Hz auditory threshold in our subject groups at baseline were similar to that in a recent survey of young adults who were not prescreened for otological abnormalities (15.5 dB [28]). Despite evidence of high-frequency auditory toxicity of quinine in healthy subjects [29], we found no increase in hearing loss due to mefloquine though, due to the testing step used, low-grade (<5 dB) changes may have been missed. Postural blood pressure responses were unaffected by mefloquine. There was, however, transient QT prolongation which, given that there is some evidence that the interaction between mefloquine and halofantrine may predispose to serious cardiac arrhythmias [30], suggests that care should be exercised when mefloquine is prescribed with other drugs known to influence ventricular repolarisation.

The present study adds to available data confirming the relative safety of prophylactic doses of mefloquine in healthy subjects. There was no clear subjective or objective evidence of mefloquine-associated neurological dysfunction or cardiovascular toxicity apart from mild transient QT prolongation. Gastrointestinal side-effects were relatively common, especially diarrhoea, but these symptoms were also mild and short-lived. Significant biochemical changes in subjects on active formulation were restricted to an average 0.5 mmol l

Table 2 Auditory threshold, systolic (SBP) and diastolic (DBP) blood pressure, and QT interval changes in the two groups. First assessment data are mean ± s.d. except for auditory threshold which are median and (interquartile range) for the average of right and left ears. The mean difference from the first assessment and 95% confidence intervals are listed for the second and third assessments.

<table>
<thead>
<tr>
<th></th>
<th>First assessment</th>
<th>Second assessment</th>
<th>Third assessment</th>
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<tbody>
<tr>
<td><strong>Mefloquine group (n=46)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing loss at 6 kHz (dB)</td>
<td>17.5 (12.0-22.5)</td>
<td>−2.5 (0, 4.5)</td>
<td>0 (−2.0, 2.0)</td>
</tr>
<tr>
<td>Fall in SBP on standing (mm Hg)</td>
<td>−1 ± 9</td>
<td>−4 (−7, 0)</td>
<td>0 (−3, 3)</td>
</tr>
<tr>
<td>Fall in DBP on standing (mm Hg)</td>
<td>−10 ± 6</td>
<td>2 (−1, 5)</td>
<td>1 (−2, 4)</td>
</tr>
<tr>
<td>QT, interval (ms)</td>
<td>404 ± 23</td>
<td>10 (4, 16)**</td>
<td>3 (1–2, 5)</td>
</tr>
<tr>
<td><strong>Placebo group (n=49)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing loss at 6 kHz (dB)</td>
<td>17.5 (13.5–25.0)</td>
<td>15 (−40, 0.5)</td>
<td>−1.5 (−3.5, 0.5)</td>
</tr>
<tr>
<td>Fall in SBP on standing (mm Hg)</td>
<td>−3 ± 8</td>
<td>−5 (0, 10)</td>
<td>3 (0, 6)</td>
</tr>
<tr>
<td>Fall in DBP on standing (mm Hg)</td>
<td>−13 ± 6</td>
<td>1 (−1, 3)</td>
<td>2 (0, 4)</td>
</tr>
<tr>
<td>QT, interval (ms)</td>
<td>404 ± 49</td>
<td>10 (−2, 22)</td>
<td>15 (1, 29)*</td>
</tr>
</tbody>
</table>

* P<0.05; ** P<0.01

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References


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