Pharmacokinetics and pharmacodynamics of mefloquine in Thai patients with acute falciparum malaria*

J. Karbwang,¹ K. Na Bangchang,² D. Bunnag,³ & T. Harinasuta⁴

A double-blind randomized comparative study of the pharmacokinetics and pharmacodynamics of a single oral dose of 750 mg or 1250 mg of mefloquine was carried out on 20 Thai male patients with acute uncomplicated falciparum malaria. In the 750-mg group, one patient exhibited an RII response, while the others responded to the treatment with a mean fever clearance time of 50.2 ± 28.2 hours and a mean parasite clearance time of 70.2 ± 17.3 hours. The main adverse effects were dizziness, nausea, vomiting, abdominal pain, and diarrhoea. Electrocardiogram monitoring detected sinus bradycardia in three patients and sinus arrhythmia in three others.

In the 1250-mg group, one patient exhibited an RII response, while the others responded to the treatment with a mean fever clearance time of 43.4 ± 36.6 hours and a mean parasite clearance time of 73.4 ± 25.2 hours. However, during the follow-up period, two patients recrudesced on day 23 and on day 31 (RII response). Dizziness, nausea, vomiting, abdominal pain, and diarrhoea were the major adverse effects, with dizziness being more frequent compared with the 750-mg group. Sinus bradycardia occurred in four patients and sinus arrhythmia in four others.

The pharmacokinetics of the two regimens were similar, with the absorption of mefloquine increasing linearly with the dose; however, vomiting within an hour of taking the drug reduced the whole blood mefloquine concentrations. The results do not indicate that there is any advantage in using a single dose of 1250 mg of mefloquine rather than 750 mg.

Introduction

From the pharmacokinetic point of view, mefloquine, one of the most successful drugs to have emerged from the U.S. Army's antimalarial drug programme, is an ideal medicament (1-6). A single oral dose has proved to be safe and active against all malaria species in humans, including multidrug-resistant falciparum malaria (7).

Despite encouraging data on the activity of mefloquine, evidence of the resistance of falciparum malaria to the drug has been increasing. For example, in a recent clinical trial at Bangkok Hospital for Tropical Diseases, the "S"-type response with a 750-mg dose of mefloquine⁸ was 85% (T. Harinasuta, personal communication, 1990), compared with a 95% cure rate in 1983 (7). The risk of mefloquine resistance developing in human malaria must be taken seriously. Administration of a higher dose of mefloquine, e.g., 1250 mg, may improve the cure rate of clinical falciparum malaria; however, it could also result in more adverse effects, and the balance between the risks and benefits should be considered. Such adverse effects, i.e., nausea and vomiting, which have been reported to affect up to 51% in patients with falciparum malaria (8-12), are the most important factor limiting the use of mefloquine. These effects are dose-related, being more likely in patients who receive higher doses, i.e., > 15 mg/kg body weight (11), and in conjunction with the nausea and vomiting caused by malaria itself can result in low plasma drug concentrations and treatment failure.

We have carried out a comparative study of the pharmacokinetics and pharmacodynamics of mefloquine⁸ given as a single oral dose of 750 or 1250 mg to Thai patients with falciparum malaria.

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Materials and methods

Patients
A total of 20 male patients with acute uncomplicated falciparum malaria (sexual form, parasitaemia <5%), aged 16–42 years and weight 45–60 kg, with no history of liver or kidney diseases, volunteered for the study. Written informed consent was obtained from all the patients, and during the study the only drug they took was mefloquine.

Each volunteer received a physical examination, routine blood tests, investigations of blood chemistry, chest X-ray, urine analysis, and an electrocardiogram (ECG), and was admitted to the Bangkok Hospital for Tropical Diseases for 42 days.

Drug administration
The patients were randomly assigned to a regimen of either 1250 mg mefloquine (five tablets) or 750 mg (three tablets). The drug was administered with a glass of water under supervision.

Blood collection for pharmacokinetic study
A 4-ml sample of whole blood was collected in heparinized tubes 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 28, and 36 hours as well as 2, 3, 4, 5, 7, 14, 21, 28, 35 and 42 days after the dose had been taken (28 samples per volunteer).

Parasite count
The parasite count was performed twice daily until negative, then once daily until day 42 of the study.

Blood tests and blood biochemistry
Blood tests and investigations of blood biochemistry were carried out weekly until day 42 of the study.

Adverse effects
All adverse reactions during the study were recorded together with the date and time when they occurred and disappeared. These reactions included gastrointestinal, central nervous system, cardiovascular, skin, and blood signs as well as any other changes that could be attributed to mefloquine.

The frequency of vomiting and of diarrhoea (number of minutes or hours after dosing) were recorded on days 0, 1, 2, 3, and 4.

A history of itching or skin rashes after taking any drugs or after taking mefloquine was noted. The intensity and duration of rashes were recorded.

ECGs and blood pressure determinations were performed at intervals when samples of blood were being taken and also weekly until day 42.

Mefloquine analysis
The level of mefloquine in whole blood was determined by high-performance liquid chromatography (HPLC) (13). The lower limit of detection of the method is 50 ng/ml mefloquine. The interassay coefficients of variation for blood samples that contained a known quantity of the drug were 4.2% for 100 ng/ml and 5.7% for 600 ng/ml mefloquine.

Pharmacokinetic analysis
The area under the whole blood concentration–time curve (AUC) was calculated using the trapezoidal rule. To estimate the area from the last sampling time to $t_{\infty}$, the first-order elimination rate constant and the half-life ($t_{1/2}$) were calculated by conventional methods (14). The mean residence time ($MRT$) was calculated from the expression:

$$MRT = \int_{0}^{\infty} t \cdot C(t) dt/\int_{0}^{\infty} C(t) dt$$

where $t$ is the time in days and $C$, the whole blood concentration of mefloquine in ng/ml.

The apparent volume of distribution under steady-state conditions ($V_{dss/f}$) was calculated from the expression:

$$V_{dss/f} = \text{Dose} \times AUMC/(AUC)^2$$

where $AUMC$ is the area under the plot of drug concentration–time versus time to $t_{\infty}$, and the systemic clearance ($Cl/f$) was obtained from the expression:

$$Cl/f = \text{Dose}/AUC$$

Statistical analysis
Statistical analysis was carried out using the Mann–Whitney U-test for unpaired samples.

Results
The clinical data on admission and baseline laboratory findings were comparable for the 10 patients who received 750 mg and the 10 who received 1250 mg of mefloquine (Table 1). There were no significant drug-related differences in the haematological parameters or the results of the biochemical investigations.

In the 750-mg group one patient exhibited an RII response, while the other nine patients responded to the treatment with a mean fever clearance time of 50.2 ± 28.2 hours and a mean parasite clearance time of 70.2 ± 17.3 hours. The main adverse effects were dizziness, nausea, vomiting, abdominal pain, and diarrhoea. ECG monitor-
Pharmacokinetics and pharmacodynamics of mefloquine

Table 1: Clinical data (mean ± S.D.) on admission, fever clearance times (FCT), and parasite clearance times (PCT) for study patients with falciparum malaria who received mefloquine

<table>
<thead>
<tr>
<th>Dose</th>
<th>750 mg</th>
<th>1250 mg</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>21.2 ± 4.0</td>
<td>28.3 ± 6.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>49.4 ± 3.9</td>
<td>52.5 ± 4.8</td>
</tr>
<tr>
<td>Haemoglobin level (mg/dl)</td>
<td>13.3 ± 2.9</td>
<td>12.5 ± 1.9</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>35.2 ± 9.3</td>
<td>39.5 ± 6.0</td>
</tr>
<tr>
<td>White blood cell count (per μl)</td>
<td>4850 ± 980</td>
<td>5090 ± 1774</td>
</tr>
<tr>
<td>Parasite count (per μl): range</td>
<td>738–18800</td>
<td>175–163060</td>
</tr>
<tr>
<td>FCT (hours)</td>
<td>50.2 ± 28.2</td>
<td>43.4 ± 36.6</td>
</tr>
<tr>
<td>PCT (hours)</td>
<td>70.2 ± 17.3</td>
<td>73.4 ± 25.2</td>
</tr>
</tbody>
</table>

The maximum concentration ($C_{max}$) and the whole blood concentration of mefloquine on day 14 in recrudescent patients were significantly different from those who exhibited a sensitive response (mean ± S.D., 318 ± 87 ng/ml in the recrudescent group; and 584 ± 183 ng/ml and 384 ± 220 ng/ml, respectively, among patients who responded to treatment in the 1250-mg and 750-mg groups).

Mefloquine concentrations in patients both with or without cardiovascular symptoms (bradycardia or sinus arrhythmia) were similar, i.e., these symptoms were not dependent on the blood concentration of the drug.

Although there was considerable inter-individual variation in the pharmacokinetic parameters, the $C_{max}$ and $AUC$ of patients who vomited within 1 hour of receiving the drug were significantly lower than those who did not vomit (Fig. 1).

Comparison of the pharmacokinetic parameters for the two dose groups indicates that the $AUC$ was greater with the higher dose (22.87 ± 6.11 μg·day·ml$^{-1}$ versus 14.80 ± 4.42 μg·day·ml$^{-1}$); however, because of marked inter-individual variability, the $C_{max}$ values (which would have been expected to be higher with the 1250-mg dose) were not statistically different. The pharmacokinetic parameters obtained are shown in Table 3.

Table 2: Comparison of the side-effects in patients who received 1250 mg or 750 mg of mefloquine (10 patients in each group)

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Dose</th>
<th>1250 mg</th>
<th>750 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Sinus arrhythmia</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Comparison of the pharmacokinetic parameters (mean ± S.D.) for the 1250-mg and 750-mg doses of mefloquine for patients who did not vomit

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Dose</th>
<th>1250 mg</th>
<th>750 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean residence time (days)</td>
<td>15.96 ± 2.58</td>
<td>16.15 ± 15.82</td>
<td></td>
</tr>
<tr>
<td>$C_{max}$ (ng/ml)</td>
<td>2411 ± 844</td>
<td>1885 ± 388</td>
<td></td>
</tr>
<tr>
<td>$t_{max}$ (hours)</td>
<td>16.1 ± 7.4</td>
<td>14.1 ± 5.8</td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-24}$ (μg·day·ml$^{-1}$)</td>
<td>22.87 ± 6.11</td>
<td>14.80 ± 4.42</td>
<td></td>
</tr>
<tr>
<td>$V_{max}$ (l/kg)</td>
<td>18.36 ± 3.42</td>
<td>25.27 ± 9.75</td>
<td></td>
</tr>
<tr>
<td>$Cl/f$ (ml·min$^{-1}$·kg$^{-1}$)</td>
<td>0.798 ± 0.230</td>
<td>0.722 ± 0.287</td>
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</tbody>
</table>

* Statistically significant difference from the value with the 750-mg dose at the $P < 0.05$ level (Student's t-test).
Discussion

No improvement in treatment outcome resulted from using a 1250-mg rather than a 750-mg dose of mefloquine. Although the therapeutic concentration of mefloquine has not yet been determined, usually a single dose of 15 mg/kg body weight is adequate. In situations where resistance is a problem, a higher dose may be required. Although the $C_{\text{max}}$ and whole blood concentrations of mefloquine on day 14 for patients with sensitive responses were significantly greater than those who exhibited resistance, the differences should be re-evaluated in a larger-scale study.

Adverse effects, including dizziness and diarrhoea, were more numerous with the higher dose (Table 2). However, the incidence of nausea and vomiting did not increase with the higher dose; this is in contrast to the results of an earlier study (11), where vomiting was found to be more common when the dose of mefloquine exceeded 750 mg. The sample size in the present study was too small to detect any dose-dependent differences and to comment on the discrepancy; nevertheless, in one larger study involving 100 patients (T. Harinasuta & D. Bunnag, personal communication, 1990), the incidence of vomiting was dose-related.

Vomiting is one of the main side-effects of mefloquine, and its incidence has been reported to be as high as 51% (10). The present study showed that vomiting within an hour of receiving mefloquine (four patients) was associated with significantly lower whole blood concentrations of the drug ($C_{\text{max}}$ and $AUC$) relative to patients given the same dose but who did not vomit (Fig. 1). This suggests that absorption of the drug was not yet complete 1 hour after its ingestion. However, one patient who vomited 3 hours after receiving mefloquine had a $C_{\text{max}}$ and $AUC$ similar to those of patients who did not vomit. This probably indicates that only vomiting within an hour requires a repeated dose. Further studies should, however, be carried out to investigate this.

Sinus bradycardia was observed in 35% of the patients in the study, and has been frequently reported in investigations of the effects of mefloquine (7–9, 15). As a result, co-administration of mefloquine and beta-blockers may require close observation.

Probably the most important adverse effect associated with mefloquine is a propensity to induce two types of dysfunction of the central nervous system. The first—a sensation of light-headedness and dysphoria often accompanied by dizziness, difficulty in concentrating, and nausea, which occurs within 6 hours of taking the drug—usually resolves within a few days (but is on occasion protracted).

Dizziness was observed for seven patients in the present study, six being in the 1250-mg group. These symptoms did not correlate with blood concentrations of mefloquine, although they were associated with the higher dose. This finding is consistent with the results of other workers (16). The second type of reaction—a more serious abrupt psychosis—often occurs in the second week after taking the drug. In one investigation of over 1000 patients, eight cases of neuropsychiatric disturbances were observed (7 and T. Harinasuta, personal communication, 1990). This adverse effect should be taken seriously since its frequency appears to be increasing (16, 17), and the reporting of its occurrence should be encouraged.

The pharmacokinetic parameters for the two doses studied were similar, except for the $AUC$ values, which were greater for the higher dose. These values increased in proportion to the dose, which suggests that absorption of mefloquine increases linearly with the dose (Table 3, Fig. 1).

The pharmacokinetic parameters obtained are in accord with those found in previous studies of patients with uncomplicated falciparum malaria (2–6, 18), for whom the value of $t_{1/2}$ was less than that of normal healthy subjects (1, 18–23). The lower value of $t_{1/2}$ may be caused by a decrease in the enterohepatic recirculation of mefloquine in patients with malaria, and consequently greater faecal clearance (4–6, 16, 24, 25). However, completely the opposite findings were found in a recent study (26), where the patients recruited were severely ill. This difference perhaps arose partly because the disease was milder in the present study.

Acknowledgements

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Résumé

Pharmacocinétique et pharmacodynamique de la méfloquine chez des malades thaïlandais atteints de paludisme aigu à falciparum

La méfloquine s’est montrée efficace contre le palu-
disme à falciparum polypharmacorésistant. Cependant, les taux de guérison diminuent. En conséquence, nous avons effectué une étude randomisée, en double aveugle, chez 20 malades thailandais de sexe masculin, atteints de paludisme aigu à falciparum non compliqué (parasitémie <5%) pour comparer la pharmacocinétique et la pharmacodynamique de doses orales uniques de 750 mg (10 malades) et de 1250 mg (10 malades) de méfloquine.

Au total, 28 échantillons de sang total pour mesure des concentrations de méfloquine ont été prélevés chez chaque malade pendant la période d'étude, soit 42 jours, à des intervalles variés après administration du médicament. Des numérations parasitaires ont été effectuées deux fois par jour jusqu'à ce qu'elles soient négatives, puis une fois par jour jusqu'au quarante-deuxième jour. Les effets secondaires ont été surveillés en questionnant les malades et en les soumettant à un examen physique, à un électrocardiogramme (ECG) et à des examens de laboratoire (hématologie et biochimie sanguine), au moment de leur admission et à diverses reprises pendant la durée de l'étude.

Dans le groupe à 750 mg, un malade a présenté une réponse de type RI. Les neuf autres malades ont répondu au traitement avec un temps moyen de disparition de la fièvre de 50,2 ± 28,2 heures et un temps moyen de disparition des parasites de 70,2 ± 17,3 heures. Les principaux effets secondaires ont été des vertiges, des nausées, des vomissements, des douleurs abdominales et de la diarrhée. Les ECG de contrôle ont montré des bradycardies sinusoales chez trois malades et une arythmie sinusoale chez trois autres.

Dans le groupe à 1250 mg, un malade a présenté une réponse de type RI. Les autres malades ont répondu au traitement, avec un temps moyen de disparition de la fièvre de 43,4 ± 36,6 heures et un temps moyen de disparition des parasites de 73,4 ± 25,2 heures. Cependant, pendant la période de suivi, deux malades ont eu une recrudescence au vingt-troisième et au trente et unième jour (réponse de type RI). Des vertiges, des nausées, des vomissements, des douleurs abdominales et de la diarrhée étaient les principaux effets secondaires du traitement. Une bradycardie sinusoale a été observée chez quatre malades et une arythmie sinusoale chez quatre autres.

La pharmacocinétique de ces deux posologies était semblable, un seul paramètre, l'aire sous la courbe de concentration en méfloquine dans le sang total en fonction du temps, étant significativement plus grand dans le groupe à 1250 mg. L'absorption de la méfloquine augmentait de façon linéaire avec la dose; cependant, des vomissements précoces ont diminué la concentration du médicament dans le sang total.

Ces résultats ne montrent pas qu'il y ait un avantage quelconque à utiliser une dose unique de 1250 mg de méfloquine plutôt qu'une dose de 750 mg.

References
on Malaria, Chiangmai, Thailand, 18–20 October 1989.