Single-dose kinetics of mefloquine in Brazilian male subjects

J. M. de Souza,¹ P. Heizmann,² & D. E. Schwartz²

Ten male subjects from a region of the state of Pará, Brazil, where malaria is endemic received a single oral dose of 1000 mg mefloquine. The plasma levels of the drug and of its metabolite, 2,8-bis(trifluoromethyl)-4-quinolinecarboxylic acid, were determined densitometrically on thin-layer chromatography plates. The pharmacokinetic parameters obtained fell within the range of values reported previously for Africans and Caucasians.

The study was conducted according to the guidelines laid out in the declaration of Helsinki and organized as part of a double-blind trial of mefloquine and sulfadoxine-pyrimethamine sponsored by WHO at Barros Barreto Hospital, Belém, Pará State, Brazil. The clinical results obtained have already been reported (7). Here, we compare the pharmacokinetic parameters for mefloquine determined in the Brazilian subjects from a malaria-endemic area with those previously reported for Caucasian and African volunteers (2).

MATERIALS AND METHODS

Subjects and administration of the drug

Ten male subjects aged 19–50 years, who weighed between 50 and 68 kg, were drawn from the population living in an area of the state of Pará in the north of Brazil that is known to be endemic for malaria. Three of the subjects (M1, M4, and M14) were slide-positive for the trophozoites of *Plasmodium falciparum* on the first 2 days of the trial. These individuals, however, did not show acute symptoms of malaria, possibly because they were "semi-immune". In addition they were not suffering from other acute or debilitating diseases and had normal plasma albumin values (3). Furthermore, none of the participants had received any antimalarial drug during the 4 weeks preceding the trial. Characteristics of the study are given in Table 1.

Excluded from the trial were:

—subjects suffering from a deficiency of glucose-6-phosphate dehydrogenase, haemoglobinopathy, malnutrition, gastrointestinal disorders, impaired liver or kidney functions, cardiovascular diseases, or any serious infections; and
—alcoholics or drug addicts.

Mefloquine, as the hydrochloride, was administered in tablet form. Each tablet contained an amount

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the subjects in the trial</th>
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<tbody>
<tr>
<td><strong>Characteristic</strong></td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>Height (m)</td>
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</tbody>
</table>

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equivalent to 250 mg drug base and was given early in the morning after a light breakfast. Each subject received four tablets (a dose equivalent to 1000 mg mefloquine base), which were taken with a glass of water.

Collection of blood samples

Blood samples (10 ml) were collected from each subject before administering the drug, and subsequently 1, 2, 3, 4, 5, 6, 7, 14, 21, 28, 35, 42, 49, 56, and 63 days thereafter. Samples were collected in tubes containing a mixture of ammonium and potassium oxalate, and were inverted ten times to ensure thorough mixing. The tubes were centrifuged for 15 minutes at 1000 g within 1 hour of sample collection and the plasma was transferred to clean glass tubes. Samples of plasma thus obtained were stored at −20 °C until analysed.

Analysis

Plasma specimens were thawed at room temperature, heated for 10 minutes in a water-bath at 37 °C, while the tubes were inverted several times by hand, and extracted as previously described (4). Extracts were analysed by thin-layer chromatography (TLC) (silica gel 60 F254 precoated TLC plates* activated for 15 minutes at 140 °C; mobile phase: dichloromethane–methanol–acetic acid, 80:10:10 v/v/v) and the plates were scanned at λ = 300 nm for absorption in the UV. The method has a sensitivity limit of 50 ng mefloquine per ml and its reproducibility is better than ±5% for mefloquine and its major metabolite, 2,8-bis(trifluoromethyl)-4-quinolinocarboxylic acid, over the concentration range 200–600 ng/ml and 600–1800 ng/ml, respectively.

Pharmacokinetic evaluation

Data were generally evaluated pharmacokinetically using "topfit" programs (7).

RESULTS AND DISCUSSION

Plasma level profiles for mefloquine and its metabolite for subject M17 are shown in Fig. 1 and 2, respectively, while the corresponding pharmacokinetic parameters are given in Table 2 for all 10 subjects. Values for half-lives and the area under the plasma concentration–time curves were determined using two-compartment model kinetics with weighting of individual data points.

The average weight of the Brazilian subjects was 10 kg less than that of the collective African and Caucasian volunteers examined previously (2). In spite of this difference in average weight, the mean pharmacokinetic parameters for the Brazilian subjects fall well within the range of those reported for the volunteers in (1) for the same dose and form of mefloquine (data for Brazilian subjects are given first): area under the plasma concentration-time curve (587 ± 164 µg·ml⁻¹·hour versus 608 ± 137 µg·ml⁻¹·hour), systemic clearance (31.1 ± 6.4 ml·hour⁻¹·kg⁻¹ versus 27.8 ± 6.5 ml·hour⁻¹·kg⁻¹); terminal elimination half-life (21.6 ± 5.1 days versus 22.0 ± 5.4 days). A slightly larger volume of distribution (23.2 ± 7.6 l·kg⁻¹ versus 19.4 ± 5.0 l·kg⁻¹) and a somewhat greater metabolite: mefloquine ratio (4.2 ± 1.4 versus 3.3 ± 1.0) was observed for the Brazilian subjects. The metabolite, 2,8-bis(trifluoromethyl)-4-quinolinocarboxylic acid, was eliminated from plasma (estimated average half-life, 20.2 ± 4.1 days) at a rate that is similar to that of mefloquine. However, since mefloquine itself has a long half-life, that of the metabolite may be limited by its rate of formation (flip-flop model).

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<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M10</th>
<th>M11</th>
<th>M13</th>
<th>M14</th>
<th>M17</th>
<th>M22</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td><strong>Mefloquine</strong></td>
<td></td>
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<tr>
<td>Half-life ($t_{1/2}$) (days)</td>
<td>18.8</td>
<td>19.0</td>
<td>29.9</td>
<td>21.1</td>
<td>31.0</td>
<td>21.5</td>
<td>16.7</td>
<td>23.3</td>
<td>17.8$^b$</td>
<td>17.4</td>
<td>21.6 ± 5.1 (10)$^a$</td>
</tr>
<tr>
<td>Elimination rate constant ($k$) (days$^{-1}$)</td>
<td>0.03686</td>
<td>0.03647</td>
<td>0.02318</td>
<td>0.03284</td>
<td>0.02236</td>
<td>0.03223</td>
<td>0.04150</td>
<td>0.02974</td>
<td>0.0393</td>
<td>0.0393</td>
<td>0.63389 ± 0.00567 (10)</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (µg·ml$^{-1}$·h)</td>
<td>744</td>
<td>496</td>
<td>913</td>
<td>710</td>
<td>410</td>
<td>545</td>
<td>650$^c$</td>
<td>438</td>
<td>536$^d$</td>
<td>428</td>
<td>587 ± 164 (10)</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (µg·ml$^{-1}$·h)</td>
<td>707</td>
<td>455</td>
<td>750</td>
<td>692</td>
<td>367</td>
<td>511</td>
<td>609</td>
<td>387</td>
<td>490</td>
<td>389</td>
<td></td>
</tr>
<tr>
<td>Apparent volume of distribution ($V_{app}$) (l·kg$^{-1}$)</td>
<td>16.6</td>
<td>25.0</td>
<td>18.9</td>
<td>20.6</td>
<td>41.6</td>
<td>22.5</td>
<td>16.0</td>
<td>29.6</td>
<td>20.9</td>
<td>20.6</td>
<td>23.2 ± 7.6 (10)</td>
</tr>
<tr>
<td>Systemic clearance ($CL_f$) (l·h$^{-1}$·kg$^{-1}$)</td>
<td>25.5</td>
<td>38.0</td>
<td>18.3</td>
<td>28.2</td>
<td>38.7</td>
<td>30.2</td>
<td>27.7</td>
<td>36.7</td>
<td>33.9</td>
<td>34.2</td>
<td>31.1 ± 6.4 (10)</td>
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<tr>
<td><strong>Metabolite</strong></td>
<td></td>
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</tr>
<tr>
<td>Half-life ($t_{1/2}$) (days)</td>
<td>18.0</td>
<td>19.5</td>
<td>23.5$^f$</td>
<td>19.0</td>
<td>27.6</td>
<td>18.6$^f$</td>
<td>22.2</td>
<td>21.9</td>
<td>13.9</td>
<td>20.2 ± 4.1 (8)</td>
<td></td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (µg·ml$^{-1}$·h)</td>
<td>1819</td>
<td>2777</td>
<td>1993</td>
<td>2143</td>
<td>2168</td>
<td>1978</td>
<td>1401</td>
<td>1825</td>
<td>2243</td>
<td>1905</td>
<td></td>
</tr>
<tr>
<td>Ratio of areas$^g$</td>
<td>2.57</td>
<td>6.10</td>
<td>2.66</td>
<td>3.10</td>
<td>6.07</td>
<td>3.87</td>
<td>3.62</td>
<td>3.93</td>
<td>5.77</td>
<td>4.19 ± 1.43 (8)</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Figures in parentheses are the number of subjects.

$^b$ Calculated for the period between day 14 and day 63.

$^c$ AUC$\infty$ is the area under the plasma concentration-time curve.

$^d$ Calculated from 0 to using the trapezoidal rule.

$^e$ Defined as $F \times$ dose/$AUC_{0-\infty}$: Calculated assuming complete absorption, i.e., $F = 1$.

$^f$ Defined as $F \times$ dose/$AUC_{0-\infty}$: Calculated assuming complete absorption, i.e., $F = 1$.

$^g$ Calculated for the period between days 28 and day 63.

$^h$ Defined as $AUC_{0-63}$ days (metabolite)/$AUC_{0-63}$ days (mefloquine).
ACKNOWLEDGEMENTS

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RÉSUMÉ

CINÉTIQUE D'UNE DOSE UNIQUE DE MÉFLOQUINE CHEZ DES BRÉSILIENS DE SEXE MASCULIN

 Dix adultes de sexe masculin, habitant une région de l'État de Pará (Brésil), où le paludisme est endémique, ont reçu une dose orale unique de 1000 mg de méfloquine. Les concentrations plasmatiques du médicament et de son métabolite, l'acide bis(trifluorométhyl)-2,8 quinoline-4 carboxylique, ont été déterminées par densitométrie après séparation par chromatographie sur couche mince et les paramètres pharmacocinétiques ci-après ont été obtenus.

Méfloquine

Aire sous la courbe de concentration plasmatique en fonction du temps \( (AUC_C) \): 410-913 \( \mu g.ml^{-1}.h \) (moyenne = 587 \( \mu g.ml^{-1}.h \)); volume apparent de distribution \( (V_\text{D}, \phi) \): 16,0-41,6 \( l.kg^{-1} \) (moyenne = 23,2 \( l.kg^{-1} \)); clairance générale \( (CL_G) \): 18,3-38,7 \( ml.h^{-1}.kg^{-1} \) (moyenne = 31,1 \( ml.h^{-1}.kg^{-1} \)); temps de demi-élimination finale à partir du plasma \( (t_{1/2}) \): 16,7-31,0 jours (moyenne = 21,6 jours).

Métabolite

Temps de demi-élimination à partir du plasma \( (t_{1/2}) \): 13,9-27,6 jours (moyenne = 20,2 jours). Le rapport entre les concentrations du métabolite et de la méfloquine, calculé à partir des aires sous les courbes de concentration en fonction du temps, du jour zéro au jour 63, était compris entre 2,6 et 6,1, avec une moyenne de 4,2.

Ces résultats montrent que les paramètres pharmacocinétiques de la méfloquine chez des sujets brésiliens semi-immuns s'inscrivent dans les fourchettes établies précédemment pour des sujets africains et caucasiens.

Références