Effect of oral contraceptive steroids on the clinical course of malaria infection and on the pharmacokinetics of mefloquine in Thai women

J. Karbwang, S. Looareesuwan, D. J. Back, S. Migasana, D. Bunnag, & A. M. Breckenridge

The pharmacokinetics of a single oral dose of mefloquine (750 mg) were followed in six healthy Thai women volunteers who regularly used oral contraceptive steroids (OCS) and in 12 Thai women patients with falciparum malaria, six of whom were also using OCS. Those taking the contraceptives continued to do so throughout the duration of the study (42 days). Both groups of patients responded to mefloquine with parasite and fever clearance times that were not significantly different, which suggests that the OCS had no deleterious effect on the course of the disease. Also, the pharmacokinetic parameters of mefloquine were not significantly different for the two patient groups. However, both the half-life and mean residence time of mefloquine were significantly longer in the healthy volunteers than in the patients, indicating that, although OCS had no effect on the pharmacokinetics of mefloquine, falciparum malaria did cause dispositional changes.

INTRODUCTION

Mortality and morbidity from malaria among women is greater during pregnancy, which suggests that exogenous sex hormones might play a role in the clinical course of the disease (1). If this is the case, administration of exogenous hormones, such as oral contraceptive steroids (OCS), may also affect the severity of malaria infection. The widespread use of OCS in countries where malaria is endemic may thus alter the response of women to the disease.

Some data from animal studies support the hypothesis that OCS may exacerbate malaria infection. For example, Dutta et al. (2) have reported that female rhesus monkeys treated with such steroids maintained an increased cumulative malaria parasite load. There was, however, no interference with the radical curative action of chloroquine. A similar study by Collins et al. (3) was inconclusive but suggested that the presence of a combined OCS containing ethynylestradiol plus norethisterone increased the level of parasitaemia during primary malaria infection. Also, Bray (4) described a limited field study in the Gambia that provided evidence for the enhancement of parasitaemia and impairment of the immune response to malaria in women who were taking a mixed oral contraceptive (Ovral®). The limited information available therefore suggests that OCS may have an effect on malaria infection.

There may also be an interaction between OCS and antimalarial drugs, since such contraceptives appear to alter the disposition of several drugs (5–7), and some antimalarials are relatively potent inhibitors of drug oxidation (8–11). Here, we report the results of an investigation of the pharmacokinetics of mefloquine, an effective treatment for multirad-resistant malaria (12–16), and the clinical course of malaria infection in women who were taking OCS.

MATERIALS AND METHODS

Healthy subjects

The healthy subjects were six Thai female volun-
teers aged 15–36 years (mean, 26.2 years) who were residents of the Bangkok area. All the women had been using OCS for at least 1 month, were non-smokers and non-drinkers, and had no previous history of liver or kidney diseases. The six women took no other drugs during the study, and all gave their written, informed consent before the study began.

**Patients**

Two groups of patients were included in the study. Group 1 consisted of six women who had never used an OCS, while group 2 comprised six women who had been using an OCS for at least 3 months.

Patients in both groups were >15 years of age with symptomatic falciparum malaria and blood slides that were positive for the asexual forms of *Plasmodium falciparum*. The patients were admitted to the Hospital for Tropical Diseases, Bangkok, Thailand. Written informed consent was obtained from all the patients, and the study was approved by the ethics committee of the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.

Patients were excluded from the study if they had a history of recent antimalarial treatment; were pregnant; had a history of gastrointestinal disease, liver disease, renal disease, or previous surgery to the upper gastrointestinal tract; had detectable levels of an antimalarial drug in samples of blood or urine; had an asexual parasitaemia >5%; or had impaired consciousness, jaundice, oliguria, or severe vomiting. The patients were examined clinically in the hospital before commencing therapy and all data were recorded on standard forms. The examination included determination of body weight, height, and temperature, while laboratory baseline investigations included determination of parasites counts, a full blood examination, investigation of serum chemistry, and screening for the presence of plasma quinine or mefloquine.

**Study design**

The healthy volunteers received three tablets of mefloquine, each containing 250 mg mefloquine base, and one tablet daily of a combined oral contraceptive (Eugynon®) containing 0.5 mg norgestrel and 0.05 mg ethinylestradiol.

Group 1 patients (non-OCS users with falciparum malaria) received three tablets of mefloquine, while group 2 patients (OCS users with falciparum malaria) received three tablets of mefloquine plus one tablet daily of the oral contraceptive.

Blood samples (10 ml) were collected in heparinized plastic tubes from all subjects via an indwelling intravenous catheter made of polytetrafluoroethylene kept patent with heparinized saline. Samples were taken before mefloquine was administered and 1, 2, 4, 8, 12, 24, 48, 72, and 96 hours as well as 7, 14, 21, 28, and 42 days after the dose had been taken. Plasma was separated within 30 minutes and stored at −20 °C until analysed.

Parasite counts were performed on patients twice daily until parasitaemia had cleared, and then daily until day 42 of the study. A full blood examination and a blood chemical profile were carried out on day 1, 4, 7, 14, 28, and 42 of the study. Also, patients received a full daily clinical examination for the first seven days of the study, then on day 14, 21, 28, and 42. The patients stayed in hospital for 42 days, while the healthy subjects remained in hospital on the first day of the study and then returned for clinical examination and blood sampling as scheduled. Both the healthy volunteers and the patients in group 2 continued taking one tablet daily of the OCS throughout the study.

**Determination of mefloquine**

The level of mefloquine was determined by high-performance liquid chromatography (HPLC) using a procedure described by Riviere et al. (17).

**Pharmacokinetic analysis**

The area under the plasma mefloquine concentration–time curve (AUC) was determined using the trapezoidal rule. The estimated area for the last sampling time to infinity, the first-order elimination rate constant, and the half-life (t½) of mefloquine were calculated using conventional methods. The mean residence time of the drug in the body (MRT) was calculated using the expression

\[ MRT = \frac{\int_{0}^{\infty} t \times C \, dt}{\int_{0}^{\infty} C \, dt} \]

where \( t \) is time (in days) and \( C \) is the plasma concentration of mefloquine.

The apparent volume of distribution (\( V_z \)) was calculated using the relation

\[ V_z = \frac{f \times \text{Dose} \times t_{\frac{1}{2}}}{AUC \times 0.693} \]

Since the bioavailability (f) of mefloquine is not known, a value of \( V_z/f \) was obtained.

**Statistical analysis**

Statistical analysis of the results was carried out using an unpaired Student’s t-test, analysis of variance, Tukey’s test, and Kruskal-Wallis analysis of variance of ranks.
Table 1  Mean values of selected clinical and laboratory parameters of malaria patients on admission to the study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-OCS users</th>
<th>OCS users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td>38.6±1.0</td>
<td>37.5±0.7</td>
</tr>
<tr>
<td>Parasitaemia level (counts/mm³)</td>
<td>10 658 (671–223 600)⁶</td>
<td>5858 (3190–32 400)</td>
</tr>
<tr>
<td>Erythrocyte volume fraction</td>
<td>36.0±4.9</td>
<td>26.8±2.1</td>
</tr>
<tr>
<td>White blood cell count (× 10⁶/l)</td>
<td>6317±1843</td>
<td>5950±3011</td>
</tr>
<tr>
<td>Concentration of creatinine</td>
<td>0.85±0.1</td>
<td>0.85±0.18</td>
</tr>
</tbody>
</table>

⁶ Figures in parentheses are the range

RESULTS

The six healthy female volunteers who used OCS tolerated 750 mg mefloquine well. The main side-effects were transient nausea and vomiting (three subjects) that required no treatment.

All patients with malaria infection had a history of fever that lasted 1–3 days and all but one was febrile. Mean core temperatures were 38.6±1.0 °C (group 1) and 37.5±0.7 °C (group 2).

The values of some clinical parameters and laboratory tests for the patients upon admission are presented in Table 1. The geometric mean of the parasite counts was greater and the mean erythrocyte volume fraction was higher among non-OCS users (group 1).

Upon treatment, non-OCS users exhibited fever and parasite clearance times of 51.4±37.3 hours and 61.4±12.8 hours, respectively, while those of OCS users were, respectively, 32.3±31.2 hours and 58.9±11.7 hours (difference not statistically different).

The main side-effects associated with mefloquine were nausea and vomiting (two non-OCS users and two OCS users), the latter occurring 2 hours after dosing in all cases.

There was considerable inter-individual variation in the peak plasma concentration of mefloquine, particularly among the OCS users (1164–3541 ng/ml). A large variation also occurred in the time to peak concentration, which ranged from 4 hours to 48 hours for the OCS-user healthy volunteers, from 6 hours to 24 hours for the non-OCS-user patients, and from 4 hours to 24 hours for the OCS-user patients.

No significant differences were found between the pharmacokinetic parameters for the OCS-user and non-OCS-user patients (Table 2). However, there were significant differences between the parameters for the OCS-user volunteers and those for the OCS-user patients. The healthy volunteers had a significantly longer t½ (17.8±2.8 days versus 14.6±1.2 days) and mean retention time (25.3±3.6 days versus 18.2±2.0 days) than patients.

Table 2. Mean values of selected pharmacokinetic parameters of mefloquine in healthy oral contraceptive steroid (OCS) users, in OCS-user patients, and non-OCS-user malaria patients who received a 750-mg dose of mefloquine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Volunteers</th>
<th>OCS users</th>
<th>Non-OCS users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.2±8.9</td>
<td>21.2±4.8</td>
<td>24.8±7.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>53.0±6.6</td>
<td>48.3±6.2</td>
<td>51.3±5.9</td>
</tr>
<tr>
<td>Time to peak concentration (hours)</td>
<td>20.0±16.0</td>
<td>13.7±8.6</td>
<td>18.3±8.8</td>
</tr>
<tr>
<td>Concentration (ng/ml)</td>
<td>1309±468</td>
<td>2234±1032</td>
<td>1631±614</td>
</tr>
<tr>
<td>Half-life (days)</td>
<td>17.8±2.8⁶</td>
<td>14.6±1.2</td>
<td>13.4±1.9</td>
</tr>
<tr>
<td>Area under curve (µg/ml×days)</td>
<td>22.9±8.1</td>
<td>18.2±6.1</td>
<td>18.6±3.4</td>
</tr>
<tr>
<td>Mean residence time (days)</td>
<td>25.3±3.6⁶</td>
<td>18.2±2.0</td>
<td>17.6±2.5</td>
</tr>
<tr>
<td>Vf/l (µg/kg)</td>
<td>18.5±6.4</td>
<td>19.5±5.3</td>
<td>15.8±3.7</td>
</tr>
</tbody>
</table>

⁶ Significantly greater than OCS-user and non-OCS-user patients at the P<0.05 level.

⁶ Significantly greater than OCS-user and non-OCS-user patients at the P<0.01 level.
DISCUSSION

In view of the fever and parasite clearance times, the findings from the study do not indicate that OCS had any major deleterious effect on the course of human falciparum malaria. Non-OCS users had higher mean parasitaemia levels on admission, but the duration of fever was similar for both users and non-users (1–3 days). These results differ from those of Bray (4), who reported that women who took OCS (Ovral®) had an impaired immune response to malaria and enhanced parasitaemia. These discrepancies may reflect differences in the duration of the OCS use or population characteristics. Patients in the present study took OCS intermittently for 3 months to 1 year only. Also, there are considerable differences between the natural history and immune status of malaria in the Gambia and Thailand. Gambian adults are mostly highly immune (18), while Thais have, at most, partial immunity. The findings of the present study should, however, be verified using a larger number of patients who have been taking OCS for a longer duration.

The pharmacokinetic parameters of mefloquine were comparable in both OCS-user and non-OCS-user patient groups, which suggests that such contraceptives may not have any major effect on the pharmacokinetics of mefloquine in patients with falciparum malaria.

The mean terminal half-life (P≤0.05) and mean residence time (P≤0.01) of mefloquine were longer in healthy subjects than in the OCS-user patients (Table 2). These differences probably arise because of malaria infection, since both groups were OCS users and the only difference between them was that the patients had malaria. These data are consistent also with previously reported findings on the pharmacokinetics of mefloquine in male volunteers and malaria patients (19).

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RÉSUMÉ

EFFETS DES CONTRACEPTIFS STÉROIDIENS ORAUX SUR L’ÉVOLUTION CLINIQUE DU PALUDISME ET SUR LA PHARMACOCINÉTIQUE DE LA MÉFLOQUINE CHEZ LES FEMMES THAÏLANDAISES

On a étudié la pharmacocinétique d’une dose unique de 750 mg de méfloquine administrée à six femmes thaïlandaises en bonne santé âgées de 15 à 36 ans qui utilisaient régulièrement des contraceptifs stéroïdiens oraux et à 12 femmes de plus de 15 ans atteintes de paludisme à falciparum, dont six prenaient également des contraceptifs oraux. Les femmes qui prenaient la pilule ont continué à la prendre pendant toute la durée de l’étude (une pilule par jour, contenant 0,5 mg de norgestrel et 0,05 mg d’éthinyless-tradiol). On a effectué des prélèvements de sang (10 ml) avant d’administrer la méfloquine puis 1, 2, 4, 8, 12, 24, 48, 78 et 96 heures et 7, 14, 21, 28 et 42 jours après administration. Les concentrations de méfloquine ont été déterminées par chromatographie liquide à haute performance (HPLC).

Le temps nécessaire à la disparition des parasites et de la fièvre n’a pas été significativement différent d’un groupe de patientes à l’autre, ce qui indique que la prise de contraceptif n’a pas eu d’effet défavorable sur l’évolution de la maladie. De plus, on n’a observé aucune différence importante entre ces deux groupes en ce qui concerne les paramètres pharmacocinétiques de la méfloquine qui ont été étudiés (temps nécessaire pour obtenir la concentration maximale, concentration maximale, demi-vie biologique, aire sous la courbe représentant la concentration en fonction du temps, temps de rétention moyen, volume de distribution). Par contre, la demi-vie et le temps de rétention moyen de la méfloquine ont été significativement plus longs chez les volontaires en bonne santé que chez les malades (17,8 ± 2,8 jours contre 13,4 ± 1,9 jours pour la demi-vie; 25,3 ± 3,6 jours contre 17,6 ± 2,6 jours pour le temps de rétention), ce qui montre que, si les contraceptifs oraux n’ont eu aucun effet sur la pharmacocinétique de la méfloquine, le paludisme à falciparum a modifié la vitesse d’élimination de cette substance.
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