Short Report: Pharmacokinetics of the Antimalarial Drug Piperaquine in Healthy Vietnamese Subjects

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Abstract. We compared plasma maximum concentration (Cmax) and area under the concentration-time curve (AUC) of the antimalarial drug piperaquine in 26 healthy Vietnamese subjects after treatment with either a single oral dose of 500 mg (n = 6) or 1,000 mg (n = 6) of piperaquine phosphate and a three-day course of 500 mg of piperaquine/day in the fasting state (n = 7) or with food (approximately 17 g fat) (n = 7). The geometric mean plasma Cmax and AUC(0–28) was 2.8-fold (200 ng/mL versus 70 ng/mL) and 1.9-fold (5,736 ng · h/mL versus 2,999 ng · h/mL), respectively, and higher in subjects receiving the 1,000-mg dose than in those receiving the 500-mg dose. The geometric mean Cmax and AUC(0–28) was 1.7-fold (198 ng/mL versus 119 ng/mL) and 1.4-fold (11,187 ng · h/mL versus 7,954 ng · h/mL) higher in the fed state than in the fasting state. Piperaquine AUC was proportional to the two doses tested and a moderate-fat meal enhanced the bioavailability of piperaquine by 41%, which should improve the therapeutic efficacy of this drug.

Until the emergence of piperaquine-resistant *Plasmodium falciparum*, the bisquinoline drug piperaquine was widely used in China in the 1970s and 1980s for malaria prophylaxis and treatment of chloroquine-resistance *P. falciparum* malaria.1 In the search for effective and safe artemisinin-based combination therapy (ACT), piperaquine is now being evaluated in Southeast Asia and Africa as a coformulation with dihydroartemisinin.2–5 Various information is required for dose optimization of ACTs. These include knowledge of the pharmacokinetics of the individual drugs so that the level of interindividual variations in blood drug concentration profiles can be determined, assessment for drug-drug interactions, and evaluation of measures that can enhance oral bioavailability.

In addition to clinical data on piperaquine,1 three studies have reported on the pharmacokinetics of this highly lipophilic, hydrophobic drug when given alone.6–8 Sim and others6 showed that piperaquine had a lengthy elimination half-life (approximately 20 days), a high volume of distribution (716 L/kg), and a low plasma clearance (1.14 L/h/kg) in eight healthy Caucasian subjects. Recently, the pharmacokinetics of piperaquine were found to be less than dose proportional and linear.6 Other pharmacokinetic studies on piperaquine have been performed in a small number of subjects treated with ACTs containing piperaquine.9–12 As yet, no in vivo drug-drug interaction study has been published on dihydroartemisinin-piperaquine.

The primary aim of the present study was to assess the plasma concentration time profiles of piperaquine after two doses of piperaquine in healthy Vietnamese subjects. The secondary aim was to determine the effect of a moderate-fat meal on the oral bioavailability of piperaquine relative to the fasting state. In an open-label study, 26 healthy male Vietnamese subjects were randomly assigned to four treatment cohorts to receive piperaquine. Cohorts 1 and 2 (6 subjects in each cohort) received a single oral dose of 500 mg and 1,000 mg of piperaquine phosphate, respectively, in the fasting state (no food for >10 h). Cohorts 3 and 4 (7 subjects in each cohort) received a multiple dose of 500 mg of piperaquine/day for three days in the fasting and fed state, respectively. For cohort 4, piperaquine was administered 10 minutes after the subjects had ingested a breakfast of noodles (90 grams of De Nhat [Instant Noodle], total fat = 16.7 grams, total protein = 9.4 grams, total carbohydrate = 65.9 grams; Acecoook Vietnam Co. Ltd., Ho Chi Minh City, Vietnam). Each tablet of piperaquine phosphate contained 250 mg salt equivalent to 144.25 mg of base (Shanghai Tiaping Pharmaceutical Co., Ltd., Shanghai, People’s Republic of China). Piperaquine tablets were administered with 200 mL of water under supervision and food was not permitted for 4 hours after drug administration for subjects in the fasting state.

The 26 subjects were judged to be healthy on the basis of medical history, clinical examination, electrocardiogram, and laboratory testing (hematology and biochemistry). Assuming a 100% difference in the area under the curve (AUC) of piperaquine between the two single doses, a standard deviation of the difference of 50%, a power of 80%, and a significance level of 0.05, we would need six subjects for each group to detect this major difference. Sims and others6 reported a marked interindividual variability of 40% in the clearance of piperaquine in the fasting state. The sample size for the multiple dose study was empirically determined as the effect of a moderate-fat meal on the exposure of piperaquine is unknown. Ethical approval for the study was obtained from the Review and Scientific Board of Central Military Hospital 108 and the Australian Defense Human Research Ethics Committee (AEC 361/04). Informed consent was obtained from all subjects before recruitment.

During the first 12 hours after drug administration, an indwelling cannula was inserted into a forearm vein and kept patent with heparinized saline. Subsequent blood samples were collected by venipuncture into heparinized tubes. Serial venous blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours and then at 2, 3, 7, 14, 21, and 28 days. For subjects on the multiple dose regimen, two additional blood samples were collected at days 42 and 56 after commencement of treatment. Plasma samples were obtained from the venous blood after centrifugation (1,500 × g for 15 minutes) and stored at −25°C until analyzed. Plasma concentrations of piperaquine were measured by high-performance liquid chromatography using the method of Lindegardh and others.13 The precision of the assay was 3% at 10 ng/mL and 4.6% at for all subjects before recruitment.

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200 ng/mL. Corresponding inaccuracy values were 3% and 2%. The lower limit of quantification for piperaquine was 2.5 ng/mL.

Noncompartmental analysis was carried out to estimate the pharmacokinetic properties of piperaquine. The rate of absorption was estimated by the maximum observed drug concentration (Cmax) and the corresponding time to reach the maximum concentration (tmax). The apparent terminal phase elimination rate constant (λz) was determined by least squares regression analysis using at least three of the last concentration data points, and the elimination half-life (t1/2) was estimated as 0.693/λz. The extent of exposure was obtained from the AUC(0–tmax) calculated by the log-linear trapezoidal method from time point zero up to 28 days after the last dose. The total AUC(0–tmax) was the composite of the AUC(0–tmax) from 0 hours to the last sample point (t) plus the quotient obtained by dividing the last measurable data point by λz. The oral clearance (CL/F) was expressed as a function of bioavailability (F) and calculated as the dose divided by AUC(0–tmax) with complete systemic bioavailability assumed (F = 1). The apparent volume of distribution (Vd/F) was calculated as (CL/F)/λz. Bioavailability with the moderate-fat meal was calculated relative to the fasting state as F = 100 × (fed AUC(0–28)/fasting AUC(0–28)). To test dose proportionality, one-way analysis of variance (for normally distributed data) or the Mann-Whitney U test (for non-normally distributed data) was applied for between-group comparisons of dose-normalized values of Cmax and AUC(0–tmax) of piperaquine.

The mean ± SD age and weight of the subjects was 20.9 ± 1.6 years and 59.3 ± 3.5 kg, and there were no significant differences in age and weight between the four cohorts of subjects. Piperaquine was well tolerated by all four treatment groups, with only mild and transient adverse events reported, which were mainly of a gastrointestinal nature. No clinically significant abnormalities in blood chemistries and individual electrocardiograms were noted before and at days 7 and 28 after piperaquine administration.

The single doses of piperaquine administered in this study (4.9 mg and 9.8 mg base/kg) were within the range used for the treatment of P. falciparum malaria (four equal doses between 2.8 and 10.8 mg base/kg). Pharmacokinetic parameters of piperaquine for the four cohorts are summarized in Table 1. The geometric mean piperaquine Cmax and AUC(0–tmax) ratios (1,000 mg/500 mg dose) were 2.8 and 1.9, respectively. When normalized against the 1,000 mg dose, there were no significant differences in the median Cmax and AUC(0–tmax) values between the two doses (P > 0.05). In contrast to our findings, Ahmed and others reported geometric mean piperaquine Cmax and AUC(0–tmax) ratios (1,000 mg/500 mg dose) of 1.1 and 1.1, respectively. When weight adjusted, the AUC of piperaquine was two-fold higher in the 1,000 mg group than in the 500 mg group of Vietnamese subjects, which suggested proportional exposure between the two single oral doses on the basis of this variable. In the subjects administered the single dose of 500 mg of piperaquine, the t1/2, CL/F, and Vd/F were 483 hours, 1.07 L/h/kg, and 748 L/kg, respectively, which are comparable to values obtained in Caucasian subjects given the same dose.

The piperaquine concentrations accumulated in plasma over the three-day course of 500 mg/day with an increase in the Cmax by 71% (70 to 119 ng/mL) and in the AUC(0–tmax) by 165% (2,999 to 7,954 ng·h/mL). Plasma piperaquine concentrations were markedly higher in the fed state than in the fasting state with an increase in the Cmax by 66% (119 to 198 ng/mL) and the AUC(0–tmax) by 41% (7,954 to 11,187 ng·h/mL). The median tmax was four hours for all treatment groups, with individual values ranging from 3 hours to 10 hours. Many subjects had secondary peaks that were commonly seen between 3 hours and 12 hours after drug administration, which suggested that piperaquine may undergo enterohepatic recycling.

The mean plasma concentration versus time profile of piperaquine in the subjects administered the three-day course with food is shown in Figure 1. The estimated mean ± SD elimination half-life in the fed subjects was 32.3 ± 7.8 days (geometric mean = 31.5 days), which was comparable to 27.8 days in malaria patients and 33 days in a healthy Caucasian volunteer. This estimate may still under-predict the true elimination half-life because the disposition phase may not have been reached even by day 7 because piperaquine exhibits multiphasic elimination.

Because the efficacy of antimalarial drugs depends on adequate oral absorption of the drug, it is most important that blood drug concentrations are above the parasitocidal concentrations long enough to suppress the growth of malaria parasites. Higher piperaquine AUC is associated with better treatment response, and day 7 plasma piperaquine concentrations are a major determinant of parasitologic failure after treatment with dihydroartemisinin-piperaquine. These

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single dose</th>
<th>Multiple dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 1, 500 mg (fasting)</td>
<td>Cohort 2, 1,000 mg (fasting)</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>69.6 (37.6–146.8)</td>
<td>195.5 (49.2–620.0)</td>
</tr>
<tr>
<td>Cmax (wt-adjust), (ng/mL/kg)</td>
<td>1.16 (0.65–2.62)</td>
<td>3.37 (0.85–10.69)</td>
</tr>
<tr>
<td>tmax (hours)</td>
<td>4 (3–4)</td>
<td>4 (3–6)</td>
</tr>
<tr>
<td>AUC(0–tmax) (ng·h/mL)</td>
<td>2,999 (1,944–3,952)</td>
<td>5,736 (705–16,884)</td>
</tr>
<tr>
<td>AUC(0–tmax) (wt-adjust), (ng·mL/kg)</td>
<td>49.9 (34.7–70.6)</td>
<td>98.9 (12.8–291.1)</td>
</tr>
<tr>
<td>AUC(0–tmax)</td>
<td>4,484 (2,535–6,459)</td>
<td>13,370 (8,844–24,422)</td>
</tr>
<tr>
<td>T1/2 (hours)</td>
<td>483 (327–626)</td>
<td>494 (416–642)</td>
</tr>
<tr>
<td>CL/F (L/h/kg)</td>
<td>1.07 (0.77–2.03)</td>
<td>0.74 (0.41–1.12)</td>
</tr>
<tr>
<td>Vd/F (L/kg)</td>
<td>748 (495–1,425)</td>
<td>525 (245–796)</td>
</tr>
</tbody>
</table>

*Fed = noodles containing approximately 17 g of fat; wt-adjust = weight-adjusted parameter.
†Median (range).
findings highlight the importance of malaria patients achieving maximum curative blood concentrations of piperaquine. Recently, Sim and others6 have shown that a high-fat meal containing 53 grams of fat coadministered with piperaquine increased the oral bioavailability of the drug by 100%. However, high-fat meals are not consumed by rural populations in Asia and Africa that are exposed to malaria infections. In Vietnam, noodles and rice are a staple component of the national diet. In the present study, we showed that a small meal of noodles containing approximately 17 grams of fat increased the oral bioavailability of piperaquine relative to the fasting state by 41%. Although malaria patients tend to be anorexic by the time treatment is initiated, they should be encouraged to take ACTs containing piperaquine with food because a moderate amount of fat markedly enhances the bioavailability of piperaquine.

In conclusion, this study showed a wide variation in plasma piperaquine concentration profiles between Vietnamese subjects given single and multiple doses of piperaquine. Of the two doses evaluated, piperaquine AUC was proportional to dose and coadministration of piperaquine with a moderate-fat meal enhanced drug absorption in healthy subjects. Because piperaquine is coformulated with dihydroartemisinin, it is recommended that patients be encouraged to take the ACT with food to improve absorption and maximize the therapeutic effect of this important antimalarial drug.

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