Sex Affects the Steady-State Pharmacokinetics of Primaquine but Not Doxycycline in Healthy Subjects

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Abstract. We evaluated whether sex affects the steady-state pharmacokinetics of the antimalarial drugs, primaquine and doxycycline, in healthy subjects. Seventeen male and 17 female healthy Vietnamese subjects were administered 30 mg (base) of primaquine daily for 14 days. After a 2-week washout period, 14 male and 14 female subjects were administered 100 mg (base) of doxycycline daily for 14 days. Women had significantly higher median values of C_{max} (212 versus 122 ng/mL, \( P < 0.001 \)) and AUC_{0-24} (1,909 versus 917 ng \cdot h/mL, \( P < 0.001 \)) of primaquine compared with men. Other than a longer \( t_{max} \) in women, no sex-related differences were seen in the pharmacokinetics of doxycycline. The primaquine pharmacokinetic data suggest that women have increased exposure to primaquine, which may put them at increased risk for toxicity when administered the same maintenance dose as men. The similar pharmacokinetics of doxycycline between the two sexes justifies the same maintenance dose.

INTRODUCTION

Primaquine, an 8-aminoquinoline, is the only drug available for the radical cure or post-exposure prophylaxis of both \textit{Plasmodium vivax} and \textit{P. ovale} malaria. To combat the spread of primaquine-tolerant \textit{P. vivax} strains in Southeast Asia, Oceania, and South America, the World Health Organization “International Travel and Health” 2005 and others recommend an adult dose of 30 mg primaquine daily for 14 days.\(^1,2\) Primaquine is also a causal prophylactic agent against the pre-erythrocytic forms of the four human species of \textit{malaria}\(^3\) and under special situations has been recommended as a chemoprophylactic agent by the US Centers for Disease Control and Prevention.\(^4\) Clinically important adverse events of primaquine use include gastrointestinal (GI) disturbances such as nausea, abdominal pain, diarrhea and vomiting, and methemoglobinemia. It is contraindicated in pregnant and lactating females and can lead to acute intravascular hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals. The frequency of adverse events seems to increase as the primaquine dose increases,\(^5\) suggesting a relationship with plasma drug concentrations.

Doxycycline, an antibiotic, given daily at 100 mg has been shown to be an effective chemoprophylactic agent in suppressing blood stages of \textit{P. falciparum} and \textit{P. vivax} malaria.\(^6,7\) There is also evidence that doxycycline possesses partial causal prophylactic activity against falciparum malaria.\(^7,9\) In combination with mefloquine, doxycycline at a dose of 200 mg once daily for 7 days is a highly effective partner drug in the treatment of multidrug-resistant \textit{P. falciparum} malaria.\(^9\) Although doxycycline is generally well tolerated, it may cause GI disturbances, photosensitivity, candidal vaginitis, and dizziness.\(^10\) Doxycycline is contraindicated in young children because of the staining of teeth and bones and in pregnant females.

The pharmacokinetics of primaquine have been well characterized in healthy subjects and malaria patients after single and multiple oral dosing.\(^12-18\) Primaquine is rapidly absorbed, reaching peak concentrations within 2–3 hours after dosing. Its plasma elimination half-life is \(\sim 7\) hours. It is a low to intermediate clearance drug with extensive tissue distribution. The metabolism of primaquine and its induced hemolysis is poorly understood. Primaquine is extensively metabolized to inert carboxyprimaquine, the major plasma metabolite, which undergoes further biotransformation to unknown metabolites that are probably more toxic than the parent compound. With the exception of carboxyprimaquine, the identification of other metabolites in humans has been difficult to pursue because the expected aminophenol metabolites and their amphoterically nature are unstable.\(^19\) Similar to primaquine, the pharmacokinetics of doxycycline has been extensively studied after single oral doses, but limited data are available on its disposition after multiple dosing.\(^20,21\) Oral bioavailability of doxycycline is high at \(\sim 95\%\), with peak concentrations being reached at 2–3 hours after dosing. Doxycycline has a plasma elimination half-life ranging from 12 to 25 hours, and it is widely distributed to body tissues. It is primarily excreted unchanged by both the renal and biliary routes, and no metabolites have been found in humans.

Despite considerable clinical experience with primaquine and doxycycline for malaria chemotherapy, there is limited information on the pharmacokinetics of both drugs between sexes. Recently, the pharmacokinetics of primaquine were found to be similar in male and female healthy subjects of Caucasian\(^22\) and Asian\(^23\) ethnicity after a single oral dose of 30 mg primaquine. In both ethnic groups, plasma primaquine concentrations tended to be marginally higher in women compared with men. However, after multiple dosing to Thai\(^24\) and Indonesian subjects,\(^22\) the oral clearance of primaquine was found to be markedly slower in women compared with men, which does not seem to be solely related to weight-based differences. Unlike primaquine, there is a paucity of information on the pharmacokinetics of doxycycline between sexes. In geriatric patients (9 men and 11 women), sex did not seem to alter the pharmacokinetics of doxycycline.\(^23\) However, in a bioequivalence study comparing two different formulations of doxycycline hyclate (Periostat and Vibramycin; 25 men and 17 women), peak plasma doxycycline concentrations were 30–38% higher in women compared with men after normalizing for body weight.\(^24\)

The aim of this study was to investigate the influence of sex on the steady-state pharmacokinetics of primaquine and doxycycline.
cycloxycline in healthy Vietnamese subjects and, if sex-related differences exist, is there a need to adjust the maintenance dose of the two antimalarial drugs.

MATERIALS AND METHODS

Subjects and study site. Thirty-four healthy Vietnamese subjects (17 men: mean [±SD] age: 25.4 [7.5] years; weight, 60.3 [6.1] kg; body mass index, 20.8 [1.5] kg/m²; 17 women: mean age: 30.0 [12.0] years; weight, 50.4 [6.6] kg; body mass index, 21.0 [2.9] kg/m²) participated in the primaquine study; and of these, 14 men and 14 women volunteered for the doxycycline study. The subjects were judged healthy based on medical history, clinical examination, and routine laboratory testing (hematology and biochemistry). Subjects were not allowed to drink alcohol or to take other medications during the 2 weeks of primaquine or doxycycline administration. The female subjects were not pregnant or lactating, and all subjects were classified as G6PD normal using the Sigma Diagnostic G6PD Kit. The Review and Scientific Board of Central Military Hospital 108 and the Australian Defense Human Research Ethics Committee (ADHREC 329/03) gave ethical approval for the study, and the subjects gave written informed consent before entering the trial.

Sample size, study design, and drug administration. Based on the Indonesian study, we expected a 48% difference in the plasma clearance of primaquine between men and women. Assuming a SD of the difference of 45%, a power of 80%, and a significance level of 0.05, we needed 15 men and 15 women to detect this major difference. The study participants received primaquine followed by a washout period of 2 weeks before receiving doxycycline. This sequential administration of drug was not randomized because no order effect was to be expected. The selection of 2 weeks of medication was based on the standard treatment period of 14 days for primaquine use as a radical cure agent or post-exposure prophylaxis against P. vivax infections. Ohrt and others also observed that most adverse events associated with daily doxycycline administration were reported within the first 14 days of starting doxycycline for malaria prophylaxis.

For the primaquine study, each subject was administered a single oral dose of 30 mg base of primaquine (four 13.2-mg primaquine phosphate tablets; Danapha, Da Nang, Vietnam) daily for 14 days. For the doxycycline study, each subject was administered a single oral dose of 100 mg base of doxycycline (115 mg doxycycline hyclate per capsule; Servidoxyne, Imexpharm, Austria) daily for 14 days. Drug was administered within 15 minutes of having a standard Vietnamese breakfast of rice, noodles, and meat. The drug was also administered with 200 mL of water. The administration of medication was observed and recorded by one of the investigators. All participants were also asked daily the non-leading question “How do you feel since you took your last primaquine tablet or doxycycline capsule?” If a subject responded affirmatively with symptoms, the timing and intensity of the complaint was recorded. The severity of the adverse events were graded on a scale of 1–3 as follows: Grade 1, mild but not affecting daily activities; Grade 2, moderate, with some interference with daily activities; Grade 3, severe, with prevention of daily duties.

Blood sampling. Venous blood samples were collected through an indwelling cannula inserted into a forearm vein and kept patent with heparinized saline. Blood samples (7 mL) were collected in lithium heparin tubes within 0.5 hours (baseline) before the last primaquine or doxycycline administration and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after drug administration. Subsequent blood samples were collected by venepuncture at 21 (for primaquine only), 24, 48, 72, and 96 hours after dosing. All blood samples were centrifuged at 1,400g for 15 minutes, and the separated plasma samples were stored at –80°C before transport to Australia on dry ice for drug analysis, which was within 12 months of collection.

Drug analysis. Plasma primaquine and carboxyprimaquine concentrations were measured by high-performance liquid chromatographic (HPLC) methods described by Mihaly and others, with minor modifications. The limit of quantification (LOQ) of primaquine was 5 ng/mL using 0.5 mL of plasma. The limit of detection of primaquine was 2 ng/mL, with a signal-to-noise ratio of 3 to 1. For carboxyprimaquine, the LOQ was 25 ng/mL using 0.25 mL of plasma. The interday assay coefficients of variation (CV%) for the measurement of primaquine at 5, 50, and 200 ng/mL were 18.7%, 4.4%, and 1.3% (N = 11), respectively. The interday assay CV% for carboxyprimaquine at 25, 250, and 1,000 ng/mL were 15.6%, 6.6%, and 2.3% (N = 27), respectively. The inaccuracy of the method at 50 ng/mL was 2% for both primaquine (N = 11) and carboxyprimaquine (N = 27).

Plasma doxycycline concentrations were measured by HPLC using a Waters 515 HPLC pump, a Waters 2487 Absorbance UV/VIS Detector set at 350 nm, and a Waters 717 Autosampler. The column used was a Zorbax SB-CN cartridge (150 × 4.6 mm, US SJOO8336; Agilent Technologies, Santa Clara, CA) with a Zorbax SB-CN USSL 002654 guard column. The mobile phase consisted of acetonitrile:0.1% trifluoroacetic (30:70, vol/vol), and the flow rate was 0.6 mL/min. Samples were prepared for analysis as follows: 0.25 mL of plasma was added to a microcentrifuge vial containing the internal standard of 0.05 mL of 5 µg/mL demeclocycyline hydrochloride (D-6140, Lot 31H0410; Sigma-Aldrich, St. Louis, MO) and 0.2 mL of 0.1 mol/L phosphoric acid. The contents were vortexed for 5 seconds and centrifuged at 14,000g for 5 minutes. The supernatant was transferred to a Vac Elute system containing a Waters ‘OASIS’ SPE cartridge, which had been activated with 1 mL of methanol. The SPE cartridge was washed with 1 mL of distilled water to waste, and the supernatant was layered onto the SPE cartridge and run to waste. The SPE cartridge was washed with 5% methanol to waste. The Vac Elute system was set to collect, and the sample was eluted using 100% methanol. The methanolic sample was evaporate to dryness using instrument grade air at 40°C and reconstituted with 0.2 mL of mobile phase. Fifty microliters was injected onto the HPLC column. The retention times for demeclocycyline and doxycycline were at ~6 and 8 minutes, respectively. The LOQ of doxycycline was 25 ng/mL using 0.25 mL of plasma. The interday assay CV% for the measurement of doxycycline (D9891, Lot 55F0201; Sigma-Aldrich) at 50, 200, 1,000, and 4,000 ng/mL were 11.8%, 8.9%, 6.9%, and 3.4% (N = 15), respectively. The inaccuracy of the method at 200 and 4,000 ng/mL was 2% and 1%, respectively.

Pharmacokinetic analysis. Maximum plasma drug concentration (Cmax), minimum drug concentration (Cmin), and time to maximum concentration (tmax) were obtained from the plasma drug concentration-time curve. The elimination rate constant (kel) was estimated by least-squares regression analysis of the post absorption and distribution log plasma drug concentration-time data using at least four points.
The elimination half-life \( (t_{1/2}) \) was calculated from the ratio \( \ln 2/k_e \). The area under the drug concentration-time curve from zero to 24 hours [AUC (0, 24)] was calculated by the mixed log-linear trapezoidal rule from the beginning of the last dose to 24 hours after the final dose. The oral clearance (CLss/F) at steady state was expressed as a function of bioavailability \( (F) \) and calculated as dose/AUC (0, 24), with complete systemic bioavailability assumed \( (F = 1) \). The apparent steady-state volume of distribution \( (V_{ss}/F) \) with complete systemic bioavailability assumed \( (F = 1) \) was expressed as a function of dose to 24 hours after the final dose. The oral clearance \( (CL_{ss}/F) \) at steady state was calculated by dividing the AUC(0, 24) of carboxyprimaquine by the AUC (0, 24) of primaquine. The pharmacokinetic parameters were calculated for each subject.

**Statistical analysis.** Data were summarized as mean ± SD or median (interquartile range [IQR]) as appropriate. Statistical comparison of pharmacokinetic parameters between men and women were made using the Mann-Whitney \( U \) test (SigmaStat version 3.0; Jandel Scientific, San Rafael, CA). The \( C_{\text{max}} \) and AUC values were log-transformed before comparison by statistical analysis, with estimated geometric mean ratio (GMR) and the 90% confidence interval (CI) for the pharmacokinetic parameters. Data were accepted as significant using the 5% significance level.

**RESULTS**

**Primaquine and carboxyprimaquine.** Four males reported mild GI disturbances that were probably associated with primaquine administration: three with abdominal pain (two with a single episode and one with a single episode over 3 consecutive days) and one with both abdominal pain and diarrhea (a single episode). Four females reported mild adverse events during their 14 days of medication. Of these, one subject had persistent diarrhea from Days 2 to 12 (two to six episodes each day) after commencement of primaquine treatment. She also had an itchy rash on her arm and body from Day 2, which persisted for 4 days. Of the other women, one had an arm rash (only reported once), one had an arm and body rash (only reported once), and one had a single episode of abdominal pain and diarrhea. No subject withdrew from the study because of adverse events experienced during the 14-day course of primaquine.

Of the 17 men, 9 were non-smokers and 8 were smokers (6–15 cigarettes/day). None of the women smoked, and none were on contraceptive medication. There were no significant differences \( (P > 0.05) \) in the pharmacokinetics of primaquine between male smokers and male non-smokers for the following parameters (median values), respectively: \( C_{\text{max}} \) of 122 and 124 ng/mL, AUC (0, 24) of 806 and 1,027 ng · h/mL, \( t_{1/2} \) of 5.6 and 6.2 hours, \( V_{ss}/F \) of 5.51 and 3.94 L/kg, and CLss/F of 0.65 and 0.51 L/h/kg.

The mean plasma concentration-time curves of primaquine and carboxyprimaquine in male and female subjects after the last daily dose of 30 mg primaquine after 14 consecutive days of medication are shown in Figure 1. The pharmacokinetic parameters of primaquine and carboxyprimaquine in men and women are summarized in Table 1. The primaquine and carboxyprimaquine concentrations were markedly higher in women compared with men. Immediately before the last dose, all female subjects had measurable concentrations of primaquine, with a median \( C_{\text{max}} \) of 18 ng/mL. In contrast to the women, only 12 men had measurable primaquine concentrations before the last dose, with a median \( C_{\text{max}} \) of 6 ng/mL. Steady-state maximum concentration \( (C_{\text{max}}) \) and exposure \( [\text{AUC (0, 24)}] \) to primaquine was ~1.7- and 2.1-fold higher, respectively, in women compared with men. The female to male GMR was 1.75 (90% CI, 1.15, 1.43) for \( C_{\text{max}} \) and 1.75 (90% CI, 1.15, 1.43) for AUC (0, 24). The \( t_{1/2} \) and \( t_{\text{max}} \) of primaquine were comparable between the two sexes at ~2.5 and 6.5 hours, respectively. Women had a significantly smaller \( V_{ss}/F \) (3.42 versus 4.59 L/kg) and a slower CLss/F (0.31 versus 0.55 L/h/kg) of primaquine compared with men.

Similar to primaquine, women had significantly higher steady-state \( C_{\text{max}} \) and \( C_{\text{ss}} \) carboxyprimaquine concentrations compared with men. The female to male GMR was 1.75 (90% CI, 1.40, 2.18) for \( C_{\text{max}} \) and 2.20 (90% CI, 0.82, 2.67) for AUC (0, 24). The \( t_{1/2} \) and \( t_{\text{max}} \) of carboxyprimaquine were comparable between the two sexes at ~2.5 and 6.5 hours, respectively. Women had a significantly smaller \( V_{ss}/F \) (3.42 versus 4.59 L/kg) and a slower CLss/F (0.31 versus 0.55 L/h/kg) of carboxyprimaquine compared with men.

**Doxycycline.** None of the subjects reported adverse events on doxycycline. There were no significant differences \( (P > 0.05) \) in the pharmacokinetics of doxycycline between male smokers and male non-smokers for the following parameters (median values), respectively: \( C_{\text{max}} \) of 3,645 and 2,662 ng/mL, AUC (0, 24) of 32,874 and 26,239 ng · h/mL, \( t_{1/2} \) of 17.9 and 24.5 hours, \( V_{ss}/F \) of 1,501 and 2,060 mL/kg, and CLss/F of 54.32 and 63.52 mL/h/kg. Mean plasma concentration-time curves of doxycycline in male and female subjects after the last daily dose
of 100 mg doxycycline after 14 consecutive days of medication are shown in Figure 2, with the pharmacokinetic properties of doxycycline summarized in Table 2. Plasma doxycycline concentrations were comparable between males and females, with median $C_{\text{max}}$ and $C_{\text{min}}$ values of ~3,150 and 710 ng/mL, respectively. The female to male GMR was 0.93 (90% CI, 0.71, 1.22) for the $C_{\text{max}}$ and 1.16 (90% CI, 0.91, 1.47) for AUC (0, 24). Females had a statistically longer $t_{\text{max}}$ compared with males (3.0 versus 1.5 hours). The median $t_{1/2}$ of doxycycline was 22.4 hours in men and 18.5 hours in women. Although women tended to have higher doxycycline concentrations compared with men, when adjusted for weight, there were no statistical differences in the CLss/F and Vss/F of doxycycline between men and women.

**DISCUSSION**

The first indication that the steady-state pharmacokinetics of primaquine may be different between men and women came from a small study in Thai subjects (four men and four women), which showed an ~2-fold higher whole blood $C_{\text{max}}$ and AUC values of primaquine in women compared with men.\(^9\) In 92 (56 men and 36 women) Indonesian subjects, who were participating in a prophylactic trial of 30 mg primaquine daily for 20 weeks,\(^2\) population pharmacokinetic analysis of sparse primaquine concentration-time data showed women to have a smaller mean Vss/F (3.45 versus 4.53 L/kg) and a slower mean CLss/F (0.31 versus 0.46 L/h/kg) compared with men, suggesting sex-related differences in the kinetics of primaquine.\(^2\) This study using rich sampling and conventional non-compartmental pharmacokinetic analysis further corroborates that women have a smaller Vss/F (3.42 versus 4.59 L/kg, $P < 0.001$) and a slower CLss/F (0.31 versus 0.55 L/h/kg, $P < 0.001$) of primaquine compared with men after multiple dosing of primaquine.

A number of reviews have examined physiological and molecular differences between sexes that may cause sex-related differences in the pharmacokinetics and pharmacodynamics of drugs.\(^26\)–\(^28\) For example, women tend to have a lower body weight, a higher percentage of body fat, lower plasma volume, higher rates of metabolism for cytochrome P450 (CYP) 3A4 substrates, and lower hepatic activity for the drug efflux transporter P-glycoprotein than men. The lack of sex-related differences in the pharmacokinetics of primaquine after a single oral dose\(^1\) may have been caused by insufficient exposure time for the physiological and molecular differences between the sexes to alter the disposition of the drug. The cause of the sex-related differences in primaquine pharmacokinetics observed at steady-state in this study is unclear.

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**Figure 2.** Mean (±SD) plasma concentrations of doxycycline versus time profiles in healthy Vietnamese subjects (14 men and 14 women) after the last dose of 100 mg doxycycline daily for 14 days.

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**Table 1**
Comparison of the median steady-state pharmacokinetics of primaquine and carboxyprimaquine in male and female healthy Vietnamese subjects after 14 daily doses of 30 mg primaquine

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Males ($N = 17$)</th>
<th>Females ($N = 17$)</th>
<th>Difference in the median values between males and females ($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primaequa $C_{\text{max}}$ (ng/mL)</td>
<td>122 (101–140)</td>
<td>212 (153–227)</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Primaequa $C_{\text{min}}$ (ng/mL)</td>
<td>6 (2–10)</td>
<td>18 (10–29)</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Primaequa $t_{\text{max}}$ (hours)</td>
<td>2.0 (1.5–3.25)</td>
<td>3.0 (2.0–3.25)</td>
<td>$P = 0.59$</td>
</tr>
<tr>
<td>AUC (0, 24) (ng · h/mL)</td>
<td>917 (749–1,047)</td>
<td>1,909 (1,558–2,168)</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Primaequa $t_{\text{1/2}}$ (hours)</td>
<td>6.1 (3.5–7.0)</td>
<td>6.8 (5.5–9.0)</td>
<td>$P = 0.07$</td>
</tr>
<tr>
<td>CLss/F (L/h/kg)</td>
<td>0.55 (0.48–0.68)</td>
<td>0.31 (0.27–0.41)</td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Vss/F (L/kg)</td>
<td>4.59 (3.37–6.45)</td>
<td>3.42 (2.74–3.87)</td>
<td>$P = 0.03$</td>
</tr>
<tr>
<td>Carboxyprimaque $C_{\text{max}}$ (ng/mL)</td>
<td>1,957 (1,608–2,321)</td>
<td>2,409 (2,141–2,793)</td>
<td>$P = 0.013$</td>
</tr>
<tr>
<td>Carboxyprimaque $C_{\text{min}}$ (ng/mL)</td>
<td>997 (823–1,342)</td>
<td>1,522 (1,278–1,752)</td>
<td>$P = 0.002$</td>
</tr>
<tr>
<td>Carboxyprimaque $t_{\text{max}}$ (hours)</td>
<td>4.0 (4.0–10.0)</td>
<td>8.0 (3.7–10.0)</td>
<td>$P = 0.78$</td>
</tr>
<tr>
<td>AUC (0, 24) (ng · h/mL)</td>
<td>36,511 (30,230–42,248)</td>
<td>47,085 (40,868–52,327)</td>
<td>$P = 0.005$</td>
</tr>
<tr>
<td>Carboxyprimaque $t_{\text{1/2}}$ (hours)</td>
<td>15.8 (13.7–19.3)</td>
<td>16.9 (15.3–17.6)</td>
<td>$P = 1.00$</td>
</tr>
<tr>
<td>AUC carboxyprimaque/ primaque</td>
<td>41.2 (38.1–53.1)</td>
<td>26.2 (20.2–35.6)</td>
<td>$P &lt; 0.001$</td>
</tr>
</tbody>
</table>
A potential source of sex-related differences in the pharmacokinetics of drugs is differences in tissue and plasma protein binding between sexes. Because primaquine binds predominately to α1-acid glycoproteins and women tend to have slightly lower plasma levels of the acute protein than men, it is unlikely that the small differences in unbound primaquine between the sexes would markedly contribute to the large pharmacokinetic differences of the drug observed in this study. Furthermore, a reduction in α1-acid glycoproteins is expected to increase unbound primaquine, with an increase in erythrocytic concentrations of primaquine and a corresponding reduction in plasma concentrations, which is contrary to the higher plasma concentrations measured in the women in this study.

Sex differences in hepatic drug metabolism seem to play a major role in sex-related pharmacokinetic differences for a number of drugs. Based on in vitro human microsomal studies, primaquine is mainly metabolized by CYP1A2 with contribution from CYP2D6 and possibly CYP3A4. Sex seems to influence CYP1A2 but not CYP2D6-mediated metabolism. Women have lower CYP1A2 activity than men, and this reduced enzymatic activity may be responsible for the higher plasma primaquine concentrations and lower clearance of the drug in women compared with men. Sex-related differences have also been reported for the disposition of other drugs that are mainly metabolized by CYP1A2 such as clozapine in the treatment of schizophrenic patients, with significantly higher concentrations (35%) of clozapine in women compared with men. The lower CYP1A2 activity in women would explain the significantly lower median metabolic ratio of carboxyprimaquine to primaquine in women compared with men [carboxyprimaquine AUC (0, 24)/primaquine AUC (0, 24): 26.2 versus 41.1]. This study also showed that cigarette smoking, which causes CYP1A2 induction and is involved in the metabolism of many drugs, does not seem to significantly alter the pharmacokinetics of primaquine.

Sex-related disparities in the pharmacokinetics and pharmacodynamics of a number of drugs have been considered as important determinants for the higher reporting of adverse drug reactions in women compared with men. Overall, female patients experience more adverse drug reactions to medications than male patients by a factor of 1.5- to 1.7-fold. The clinical implications of the higher bioavailability of primaquine in women compared with men are limited. In review articles on the efficacy and tolerability of primaquine used for chemoprophylaxis or radical cure, no mention is made of sex differences in response to the medication. However, in a small study of Australian military personnel (191 men and 23 women) deploying out of a malaria-endemic area, a higher prevalence of GI disturbances was reported in women compared with men after post-exposure prophylaxis with primaquine. It is quite possible that the higher intolerance to primaquine observed in the Australian women may be associated with higher primaquine concentrations in the women compared with men. However, in this study, men tended to report more drug-associated GI disturbances than women (24% versus 12%), but of these subjects, it was a female participant who reported the worst GI experience on primaquine, with persistent diarrhea for 10 days of the 14-day course. Noteworthy, her primaquine and carboxyprimaquine concentrations were not markedly different from the other women. Further studies of primaquine pharmacokinetic–pharmacodynamic inter-relationships are warranted to determine whether the pharmacokinetic differences observed in this study necessitates a maintenance dose conversion factor for women.

In contrast to primaquine, with the exception of 𝜏max, no sex-related differences were observed in the steady-state pharmacokinetics of doxycycline in the Vietnamese subjects. The steady-state Cmax and 𝜏max of doxycycline in this study were comparable to those reported by Shmuklarsky and others in healthy male Caucasian subjects (mean Cmax of ~3,400 ng/mL and 𝜏max of 20.8 hours) who were protected participants of a mosquito challenge study for the causal prophylactic assessment of doxycycline. However, the protected participants had a higher steady-state minimum concentration (1,022 versus 720 ng/mL), a smaller apparent volume of distribution (982 versus 1,835 mL/kg), and a slower plasma oral clearance (37.2 versus 56.4 mL/h/kg) of doxycycline compared with the Vietnamese male subjects, which may suggest ethnic differences in the disposition of doxycycline. Unlike the findings from a bioequivalence study of two formulations of doxycycline, we did not observe a difference in the Cmax of doxycycline between men and women. Based on the similar pharmacokinetics of doxycycline in men and women, the same dose regimen of doxycycline is recommended for both sexes.

In conclusion, women have a smaller apparent volume of distribution and a slower oral clearance of primaquine compared with men after multiple dosing, leading to higher maximum plasma concentrations and increased drug exposure. The increased exposure to primaquine may put women at increased risk of toxicity when administered the same maintenance dose as men. However, more information on the relationship between primaquine concentrations and the pharmacodynamic response of primaquine is needed in women before an adjustment of the maintenance dose can be rec-
ommended. Unlike primaquine, no major sex-related differences were observed in the pharmacokinetics of doxycycline, suggesting that the same maintenance dose can be used for both sexes.

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