SHORT REPORT: LACK OF SEX EFFECT ON THE PHARMACOKINETICS OF PRIMAQUINE

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Abstract. The pharmacokinetics of primaquine have been well defined in male volunteers, but there is little data on the disposition of the drug in women. We compared the kinetics of primaquine in nine male and nine female healthy Australian volunteers after the administration of a single oral dose (30 mg base) of primaquine. No statistical differences were observed in the following kinetic parameters of primaquine between men and women, respectively: maximum plasma concentration (93 ± 26 and 115 ± 38 ng/mL; 95% confidence interval [CI] of the mean difference: −55 to 10 ng/mL; P = 0.16), area under the curve (1.1 ± 0.5 and 1.2 ± 0.4 μg·h/mL; 95% CI: −0.6 to 0.3 μg·h/mL; P = 0.54), and clearance (0.34 ± 0.12 and 0.39 ± 0.14 L/h/kg; 95% CI: −0.17 to 0.08 L/h/kg; P = 0.46). The clinical relevance of such findings would suggest that sex does not have to be taken into account as a factor when prescribing primaquine for radical cure or terminal prophylaxis of Plasmodium vivax malaria.

Plasmodium vivax affects about 100 million people each year in tropical areas and is an important cause of morbidity in the Americas, the Western Pacific, and Asia.1 Primquine (Weifa A.S., Kragero, Norway), an 8-aminoquinoline, is the only drug available for radical cure and terminal prophylaxis of P. vivax. It is also a highly effective prophylactic agent against both falciparum and vivax malaria at a daily adult dose of 30 mg.2 The main side effects associated with primaquine use are gastrointestinal disturbances such as nausea and abdominal pain. Despite considerable clinical experience with primaquine, little data are available on whether there are sex differences in the tolerability and pharmacokinetics of primaquine.

Nasveld and others3 reported a higher prevalence of gastrointestinal disturbances in female than male Australian Defense Force personnel on terminal prophylaxis with primaquine. The higher prevalence of gastrointestinal disturbances reported in the Australian women may have been associated with higher plasma primaquine concentrations in the women compared with levels in men. Although the kinetics of primaquine have been well defined in male subjects,4–8 only one study has examined the pharmacokinetics of primaquine in female subjects.9 Thai women were found to have significantly higher maximum concentrations of primaquine in blood and plasma than in Thai men.

Since the Thai study revealed sex differences in the kinetics of primaquine, we determined the pharmacokinetics of primaquine at the recommended dose of 30 mg in healthy Australian female and male volunteers to ascertain whether sex differences affect the disposition of the drug. Based on the Thai study, we expected a 45% difference in the area under the curve (AUC) of primaquine between men and women. Assuming an SD of the difference of 30%, a power of 80%, and a significance level of 0.05, we needed nine men and nine women to detect this major difference. Eighteen healthy Australian Defense Force personnel (nine men and nine women) were recruited into the study. The glucose-6-phosphate dehydrogenase normal volunteers were judged healthy based on medical history, clinical examination, and routine laboratory testing (hematology and biochemistry). Ethical approval for the study was obtained from the Australian Defense Human Research Ethics Committee. Informed consent was obtained from all volunteers.

A single oral dose (30 mg) of primaquine (four primaquine diphosphate tablets of 7.5-mg base per tablet; Boucher & Muir Pty, Crows Nest, NSW, Australia) was given after a full breakfast (toast, spreads, bacon, and eggs) containing no less than 30 g of fat. 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 venepuncture into heparinized tubes. Serial venous blood samples (7 mL) were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours.

Plasma samples were obtained from the venous blood after centrifugation (1,500 g for 15 minutes) and stored at −80°C until analyzed. Plasma concentrations of primaquine were measured by high-performance liquid chromatography using the method of Mihaly and others.6 The inter-assay coefficients of variation for primaquine were 17.8% and 3.3% at 5 (N = 9) and 100 ng/mL (N = 9), respectively. The limit of quantitation of primaquine was 5 ng/mL using 0.5 mL of plasma. Non-compartmental analysis was carried out to estimate the pharmacokinetic parameters of primaquine.10 The AUC was calculated by the linear trapezoidal method, with extrapolation to infinity. Normally distributed data are expressed as mean values ± SD, with 95% confidence intervals (CIs) of mean differences for kinetic parameters between the sexes. Statistical comparisons were made using the Student unpaired t test, accepting a difference at the 5% level as significant.

The average age and weight of the male volunteers were 33.7 ± 8.7 years and 89.7 ± 5.7 kg, respectively. Corresponding values for the female volunteers were 34.0 ± 7.9 years and 70.0 ± 11.3 kg. The mean plasma concentration versus time profiles of primaquine in the male and female volunteers are shown in Figure 1. The plasma profiles of primaquine were similar between the sexes.

No significant differences were observed between the Australian male and female volunteers in the disposition of primaquine (Table 1). The mean maximum plasma concentration (Cmax) of primaquine was comparable between men and women (93 versus 115 ng/mL), with maximum concentrations being reached at about 2–3 hours after drug administration.

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When normalized against dose/weight, there were no significant differences in $C_{\text{max}}$ ($P = 0.88$) and AUC ($P = 0.56$) of primaquine between men and women. Similarly, the mean oral clearance (CL/$f$) and elimination half-life ($t_{1/2}$) of primaquine were comparable between sexes. Inter-patient variability in $C_{\text{max}}$ CL/$f$, and $t_{1/2}$ of primaquine between men and women, based on coefficients of variation, ranged between 27.5% and 35.9%. The apparent volume of distribution ($V_d/f$) of primaquine was about 4 L/kg for both sexes, suggesting extensive tissue distribution of the drug.

The findings of this study reveal that the pharmacokinetics of primaquine in the male Australian volunteers are in close agreement to those values reported by Mihaly and others in healthy male white volunteers. However, our findings were not in accord with those of Singhasivanon and others who found a difference in the kinetics of primaquine between Thai male and female volunteers. The mean plasma $C_{\text{max}}$ and AUC of primaquine were markedly higher in the Thai female volunteers (252 versus 139 ng/mL and 1.9 versus 1.3 µg.h/mL, respectively). Furthermore, the $C_{\text{max}}$ and AUC values of primaquine in the Thai study were higher than those values estimated in our study (252 versus 115 ng/mL and 1.9 versus 1.2 µg.h/mL, respectively), even though the Australian volunteers received twice the dose of primaquine. Although the weight of the Thai volunteers (range, 43–65 kg) was less than the Australian volunteers (range, 57–96 kg), body weight differences between the two groups would be insufficient to explain the markedly lower oral clearance of primaquine seen in the Thai subjects (10.65 versus 28.1 L/hr). This discordance in results is difficult to explain as the pharmacokinetics of primaquine has been reported to be similar between Thais and whites.

In conclusion, this study showed that the disposition and clearance of primaquine is comparable between healthy male and female volunteers after a single oral dose of primaquine. The clinical relevance of such findings would suggest that sex does not have to be taken into account as a factor when prescribing primaquine to young healthy people. However, further studies are required to determine whether the kinetics of primaquine and adverse events differ between the sexes when given the recommended maintenance dose of 30 mg of primaquine daily over a period of time.

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