

## Gender-specific distribution of mefloquine in the blood of healthy volunteers following the administration of therapeutic doses

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### Abstract

The distribution of the antimalarial drug mefloquine (MQ) following the administration of standard therapeutic doses (1,250 mg mefloquine in split dose) to 22 healthy Caucasian volunteers was assessed in whole blood, serum, plasma, RBCs, WBCs, and platelets using high performance liquid chromatography. Plasma MQ levels after 14, 48, and 168 hours were considerably higher in female subjects than in males, concordant with a significantly higher frequency, duration, and severity of adverse reactions. However, mean drug concentrations of RBCs tended to be higher in male volunteers. The concentrations in other blood components were similar in both genders. No correlation was seen between MQ concentrations in plasma and RBCs. Since the observations relate to healthy individuals, they do not take into account the selective uptake of MQ by *Plasmodium*-infected RBCs as in the case of therapeutic drug use. Although plasma MQ levels in female healthy volunteers are considerably higher and the concentrations of the RBC are initially lower as compared to males they do not seem to justify an adjustment of treatment guidelines for MQ in female Caucasian individuals.

**Keywords:** Mefloquine, pharmacokinetics, gender-specific distribution, plasma, red blood cell

### Introduction

The apparent incidence of adverse events (AEs) following the oral administration of the antimalarial drug mefloquine (MQ) is high, with reports of 47 to 90% of adults experiencing some type of AE (1-2). Previous studies with MQ have shown that a significantly higher frequency and severity of treatment- and prophylaxis-related adverse events (AEs) occur in female patients [14-16]. The use of high doses of MQ is also associated with higher frequencies of AEs, particularly in female patients (3-4). MQ also inhibits acetylcholinesterase and butyrylcholinesterase, the likely cause for the frequent gastrointestinal and CNS-related AEs which occur at high dosages of the drug (5). The gender-specific differences in the frequency and severity of AEs experienced following the administration of MQ in prophylactic as well as therapeutic dosages may at least in part be attributable to different distribution patterns in liquid and cellular blood compartments. The aim of the present study was to elucidate the gender-specific distribution of MQ in these compartments at therapeutic dosages of the drug in order to assess any relationship with the occurrence of treatment-related AEs. Furthermore, the eventual necessity of adjusting treatment guidelines in female patients was explored.

### Methods

The study was conducted with 22 healthy Caucasian volunteers (10 males, 12 females) aged 20 to 45 years (median age of 26) at the Department of Specific Prophylaxis and Tropical Medicine, University of Vienna. Written informed consent was obtained from all study participants and the study protocol was approved by the ethical review board at the University of Vienna. All subjects received 1,250 mg Lariam® each (Hoffmann-la Roche

Pharmaceuticals, Basel, Switzerland) as split dosages of 750 mg, followed by another 500 mg at 6 hours apart. CBCs were conducted at 14, 48, and 168 hours after the administration of the first MQ dose. All volunteers were monitored for AEs during the 21 days after the first dose had been administered. Venous blood samples were collected at 0, 14 (the estimated time to reach peak plasma concentrations, 8 hours after the administration of the second MQ dose), 48 (estimated to be the beginning of the log-linear elimination phase), and 168 (the minimum time required for therapeutic drug levels to eliminate malaria parasites) hours. MQ concentrations in whole blood, plasma, serum, RBC, WBC, and platelets) were measured using high performance liquid chromatography (HPLC) (6). Statistical analysis was performed by Non-parametric test at  $\alpha = 0.05$  for all tests.

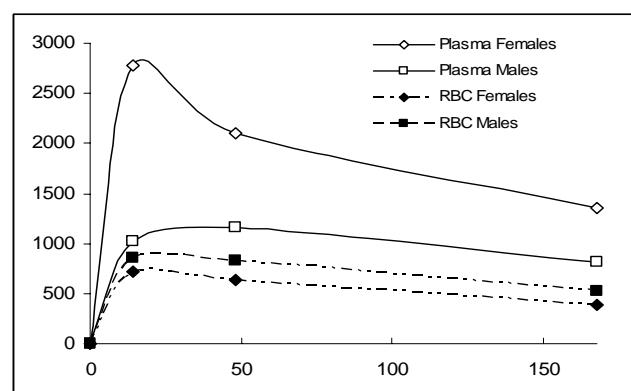
## Results

A significant higher plasma MQ concentrations was observed in female subjects at all time points, whereas RBC concentrations tended to be higher in males compared with females at 14 and 48 hr. The concentration in whole blood, serum, WBC, and platelet were similar for both genders (Table 1). This resulted in significantly higher plasma/RBC concentration in females than in males at 14 and 48 hr. Figure 1 is a graphical representation of the changes observed in the concentrations in RBCs vs plasma in males and females. MQ concentrations in RBC in both genders were significantly lower than in whole blood and serum. Platelet and WBC MQ levels were approximately 6 times higher and 20 times higher than in whole blood, respectively. No correlation was seen between plasma drug concentrations and RBC levels, suggesting that plasma levels are a poor predictor of RBC drug levels. The most commonly reported AEs were vertigo (96%), followed by nausea (82%), headache (73%), sleeping disturbances (59%), and diarrhea (41%). The overall symptom scores (OSS) reflecting the frequency, duration, and severity of drug-related AEs were significantly higher in female subjects (20.8 in males vs 43.3 in females;  $p=0.003$ ). Frequency, duration, and severity of AEs were directly correlated ( $r=0.519$ ;  $p=0.016$ ) with plasma drug levels (Figure 2).

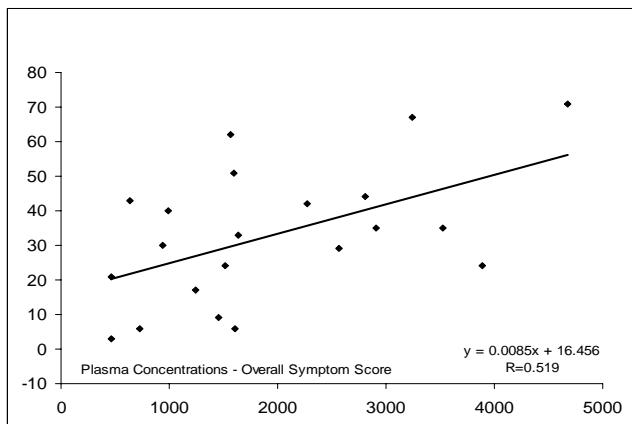
**Table 1** Mean MQ concentrations, in ng/mL, in male (n = 10) and female (n = 12) healthy volunteers at 14 hours (H14), 48 hours (H48) and 168 hours (H168) after administration of the first drug dose

Substrate	H14		H48		H168	
	Female	Male	Female	Male	Female	Male
Whole Blood	1,360	1,648	1,437	1,272	896	885
Serum	1,570	1,623	1,244	847	811	1,304
Plasma*	2,778	1,017	2,106	1,214	1,353	666
RBC*	719	857	633	827	389	375
WBC	35,641	33,885	32,414	29,449	17,584	16,214
Platelets	9,212	9,002	9,710	7,825	5,538	5,808

\* Statistically significant difference between males and females ( $p < 0.01$ ; Mann-Whitney U test)



**Figure 1** Mean MQ concentrations, in ng/ml, in (A) the serum and plasma, and (B) plasma and RBC of male and female healthy volunteers at 14, 48 and 168 hours after the administration of the first dose



**Figure 2** Scatter plot and regression line for MQ plasma concentrations (ng/mL) and overall symptom score (OSS). The frequency, duration and severity of adverse events (represented by OSS) exhibited significant correlation with mefloquine plasma levels (Spearman Rank test:  $r = 0.519$ ;  $p = 0.016$ )

## Discussion

Our data suggest that plasma concentrations are significantly higher in females and this correlated with higher frequency and severity of AEs in females compared with males. RBC drug levels at H14 and H48 are however, lower in females than in males. Since the RBCs are the site of malarial infection, this may be interpreted as a potential shortfall of therapeutic activity. However, recent investigations (7) have shown that RBCs infected with *P.falciparum* contain  $>4$  times as much MQ as compared to uninfected RBCs (8). These observations would also explain the equivalence of the therapeutic efficacy of MQ in uncomplicated infections with MQ-sensitive *P. falciparum* in both genders. The lack of any significant correlation between plasma and RBC drug concentrations suggests that MQ plasma levels may not truly represent the amount of drug reaching uninfected or parasitized RBCs. However, this would also mean that low plasma concentrations, as observed in predominantly male populations, do not automatically indicate sub-therapeutic RBC drug concentrations (9). MQ concentrations were much higher in WBCs and platelets, suggesting an active uptake of the drug into these cells. However, these levels appear to have little relevance for the treatment of malaria.

## Conclusion

The higher AE frequencies and severities caused by higher plasma levels in females in combination with lower RBC drug concentrations create speculation about the risks and benefits of MQ treatment for female patients. In spite of the considerably higher number of AEs in females, we would not recommend a down-adjustment of mefloquine treatment guidelines for these individuals.

## Acknowledgements

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