Am. J. Trop. Med. Hyg., 66(5), 2002, pp. 445–447

Dear Sir:

We read with great interest the article by E. Schwartz et al. entitled "Serious adverse events of mefloquine in relation to blood level and gender" that appeared in your journal.[1] The study included 17 patients who experienced serious adverse events, mostly related to the CNS and ascribed to the prophylactic intake of mefloquine, and 28 controls without complaints. Although females tended to be more susceptible to the occurrence of adverse effects than males, the serum concentrations of mefloquine showed no significant difference between the patients and the control group or between males and females.

It should be noted that the observations of Schwartz et al. relate to a retrospective analysis based on single time-point assays after the last mefloquine. We have performed a prospective pharmacokinetic study administering prophylactic doses of mefloquine over a period of 9 weeks to 12 healthy adult Caucasians (6 females, 6 males), using a loading dose of 250 mg mefloquine (base) on days 0 and 1.[2] Blood samples were drawn at 30, 60, 120, 240, 360, and 480 minutes after the first and second dose. Subsequently, blood sampling was done immediately before and 8 hours after the administration of the weekly doses between days 7 and 56. After the last dose, on day 63, blood samples were again taken at the shorter intervals used initially, and on days 64, 65, 68, 70, 91, and 119, i.e. until 8 weeks after the administration of the last dose. Blood plasma was used for the drug assays.

Similar to the observations of Schwartz et al., adverse reactions were significantly more frequent in females than in males. However, in female subjects, mean $C_{min\text{-}ss}$, $C_{max\text{-}ss}$, and $AUC_{d\ 400–35}$ were significantly higher than in males, while the mean V_{ss} in females was narrower, even after adjusting for body weight.

The difference between the results may be due to fact that Schwartz et al. measured single mefloquine concentrations at different intervals after the observed adverse effects and the last dose. As can be seen from our study, the mean plasma

concentrations of males and females exhibit a distinct convergent tendency from one week after the last dose, apparently due to similar clearance in both genders. Such details can best be recognized in a longitudinal pharmacokinetic study with regular blood sampling at relatively short intervals, but are hardly detectable in a retrospective concentration point study that does not lend itself to the determination of volume of distribution and clearance.

In the absence of reliable information on the partition of mefloquine between the various blood components, it is difficult to say to what degree differences between serum and plasma concentrations may have contributed to the dichotomy between our observations and those of Schwartz et al.

It may also be too early for concluding that mefloquine levels are not different between subjects with or without adverse effects. Conclusive investigations of a potential interdependence between mefloquine concentrations and the occurrence and/or severity of adverse events require a prospective study of considerable size due to the wide diversity of individual disposition to such events. Before embarking on a study of this type it would be useful to explore the hitherto little-known determinants of individual disposition to and manifestation of adverse events.

REFERENCES

1. Schwartz E, Potasman I, Rotenberg M, Almog S, Sadetzki S, 2001. Serious adverse events of mefloquine in relation to blood levels and gender. *Am J Trop Med Hyg 65:* 189–192.
2. Kollaritsch H, Karbwang J, Wiedermann G, Mikolasek A, Na-Bangchang K, Wernsdorfer WH, 2000. Mefloquine concentration profiles during prophylactic dose regimens. *Wien Klin Wochenschr 112:* 441–447.

GERHARD WIEDERMANN, MD
Department of Specific Prophylaxis and Tropical Medicine
Institute of Pathophysiology, University of Vienna
Kinderspitalgasse 15
A-1095 Vienna, Austria
Tel: +43-1-405-7122
Fax: +43-1-403-8343-90

HERWIG KOLLARITSCH, MD
Department of Specific Prophylaxis and Tropical Medicine
Institute of Pathophysiology, University of Vienna
Kinderspitalgasse 15
A-1095 Vienna, Austria
Tel: +43-1-40490-64850
Fax: +43-1-403-8343-90
Email: herwig.kollaritsch@univie.ac.at

MICHAEL KUNDI, MD
Institute of Environmental Hygiene
University of Vienna
Kinderspitalgasse 15
A-1095 Vienna, Austria
Tel: +43-1-4277-64726
Fax: +43-1-4277-9647
Email: michael.kundi@univie.ac.at

WALTHER H. WERNSDORFER, MD
Department of Specific Prophylaxis and Tropical Medicine
Institute of Pathophysiology, University of Vienna
Kinderspitalgasse 15
A-1095 Vienna, Austria
Tel: +43-1-879 7015
Fax: +43-1-803-8343-90
Email: walther.h.wernsdorfer@univie.ac.at