ABSTRACT

To determine the relative bioequivalence of the commercial tablet formulations of mefloquine (Lariam®, the reference product, Mephaquin® and Eloquine®), a pharmacokinetic study was conducted among 27 adult male Thai patients with uncomplicated falciparum malaria in Bangkok and in Mae Sot, Tak Province, Thailand on June 1997-August 1998. The patients were given one of the three tablet formulations of mefloquine (MQ), 750 and 500 mg (25 mg/kg body weight) at 24 and 30 h after a single oral 300 mg dose of dihydroartemisinin (DHA). Whole blood mefloquine concentrations were assayed by HPLC. The therapeutic effect of the combination antimalarial regimen was also evaluated.

The absorption profile of the three tablet formulations of mefloquine were significantly different. Lariam® was absorbed most rapidly and most extensively (median C_{max}: 3,460 ng/ml; AUC_{0-48h}: 4.67 μg.day/ml; AUC_{0-7d}: 11.91 μg.day/ml; AUC: 45.87 μg.day/ml). Eloquine® had comparable C_{max} and AUC during the first 2 and 7 days of treatment, while total AUC was lower (p=0.05) compared with Lariam® (median C_{max}: 3,310 ng/ml; AUC_{0-48h}: 4.57 μg.day/ml; AUC_{0-7d}: 9.56 μg.day/ml; AUC: 26.79 μg.day/ml). The ratios of mean C_{max} and AUC of Eloquine® to Lariam® are 93.2% and 75.9%, respectively. Mephaquin® had the lowest rate and extent of absorption (median C_{max}: 2,410 ng/ml; AUC_{0-48h}: 3.54 μg.day/ml; AUC_{0-7d}: 9.08 μg.day/ml; AUC: 22.48 μg.day/ml). Mean C_{max} and AUC with this tablet formulation were 67.4 and 53.8% of that of Lariam®, and 72.4% and 70.9% of that of Eloquine®. Other pharmacokinetic parameters such as t_{max}, $t_{1/2z}$ and MRT

were not significantly different among the three groups (median t_{max}: 12 h; $t_{1/2z}$: 10.95- 13.4 d; MRT: 15.55- 16.7 d). Mephaquin® was considered bioinequivalent to both Lariam® and Eloquine®. The latter was also considered bioinequivalent to the reference formulation, Lariam®. The results of this study confirm previous findings of bioinequivalence between Mephaquin® and Lariam® in cross-over studies among healthy volunteers. The significant difference in absorption profiles among the three tablet formulations of mefloquine needs to be considered in choosing a tablet formulation to be used especially in areas with increasing *P. falciparum* resistance to mefloquine.

The combination DHA/MQ regimen was effective in rapidly clearing the infection, and was generally well-tolerated. Over-all reduction in parasitaemia in 24 h (effect of only DHA) was 99.8% (range: 82.5-100%), while mean (SD) PCT and FCT were 39 (19.8) h and 30 (24) h, respectively, for all groups combined. The cure rate was 65.2- 78.3% (15- 18/23 evaluable cases) at 42 days of follow-up. There were no RII or RIII responses. All recrudescences occurred among patients in Mae Sot from 14 to 28 days after treatment. Whole blood concentrations at the time of recrudescence ranged from 360 to 1,409 ng/ml (median: 562 ng/ml). Patients with treatment failure had lower whole blood mefloquine concentrations during the first 6 days after treatment. Day 6 mefloquine levels were predictive of treatment outcome. Adverse effects such as dizziness, nausea, vomiting, abdominal pain and diarrhoea were observed in 11-44% of patients after mefloquine administration, and resolved without specific medication after 1-3 days. One case of neuropsychiatric adverse effect, i.e. seizure-like episode, severe anxiety and insomnia, occurred 5 days after

treatment with DHA/ Mephaquin® and resolved by day 49. There were no significant haematological or serum biochemical adverse effects.

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