

Population Pharmacokinetics of Mefloquine for Malaria Prophylaxis in Australian Soldier Deployed in East Timor

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Background:

Malaria is a deadliest parasitic infection in the world with annual infections of about 500 million people and 1.5-2.7 million deaths. Due to increasing number of drug resistant malaria, mefloquine was then introduced. Several pharmacokinetics studies on mefloquine were carried out previously, but none of these studied the population pharmacokinetics of mefloquine in soldiers in the field.

Objective: To study the population pharmacokinetics of mefloquine for malaria prophylaxis in Australian soldiers deployed in East Timor in field conditions

Method: The soldiers were on weekly mefloquine prophylaxis for 26 – 28 weeks. Following 3 daily loading doses of 250 mg mefloquine base (Lariam) each, oral weekly maintenance of doses of 250 mg were taken by each soldier during military deployment between October, 2000 and April, 2001. The soldiers comprised 154 males and 7 females with a mean (range) weight of 81 kg (53 – 135 kg), height of 177 cm (157 – 192 cm), and age 26 years (18 – 51). Blood sampling was performed after the last dose of the loading dose and at week 4, 8 and 16 during maintenance dosing. Mefloquine concentrations were measured by HPLC. Population pharmacokinetic modeling was performed using NONMEM.

Result: A one-compartment model was found to be adequate to describe the mefloquine concentration data. A NONMEM analysis resulted in a population model being developed with inter-occasion variability (IOV) included. The typical population values for clearance (CL), volume of distribution (V) and first-order absorption rate constant (KA) were 1.78 Lh⁻¹, 734 L, 0.41 h⁻¹, respectively. Although weight and sex influenced V, none of these factors had sufficient impact to warrant any dosing changes. The interindividual variability (coefficient variation, CV%) for CL and V were 24.4% and 19.3%, respectively. The IOV for those parameters were 20.8% and 9.5%, respectively. The absorption and elimination half-lives were 1.7 hours and 11.9 days, respectively. The maximum, minimum and average steady state concentrations were 887.6 ng/ml, 609.4 ng/ml and 762.4 ng/ml, respectively. The residual variability was 13.3%

Conclusion: The population pharmacokinetics of orally administered mefloquine prophylaxis have been described with sparse data obtained from Australian soldiers under field conditions. All pharmacokinetic parameters were quite similar with previous non-population studies. This finding reinforces the use of loading dose of 250 mg mefloquine for three days and 250 mg weekly thereafter.

Keywords: population pharmacokinetics; malaria; prophylaxis; NONMEM; mefloquine
