

Piperaquine pharmacokinetics during intermittent preventive treatment for malaria in pregnancy

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Objectives & Methods :

Objectives: Pregnant women are at higher risk of *Plasmodium falciparum* infection and pregnancy-specific adverse effects. WHO suggests that intermittent preventive therapy in pregnancy (IPTp) should start in the second or third trimester and continue until delivery. Several pharmacokinetic studies have shown that dose adjustment may not be needed for the treatment of malaria in pregnancy with Dihydroartemisinin-Piperaquine (DP). Therefore, this study aimed to evaluate the population pharmacokinetics of piperaquine given as IPTp in pregnant women.

Methods: Pregnant women were enrolled in clinical trials conducted in Kenya and Indonesia [1, 2] and treated with standard 3-day course of DP, administered in 4-8 weeks intervals from the second trimester until delivery. Pharmacokinetic blood samples were collected sparsely for piperaquine drug quantification before each treatment round, at the time of breakthrough of symptomatic malaria, and at delivery. Piperaquine population pharmacokinetic properties were investigated using nonlinear mixed-effects modelling. The **\$PRIOR** functionality in NONMEM was used to stabilise the model performance. A previously published population pharmacokinetic model, describing DP in the treatment of uncomplicated *falciparum* malaria in pregnant women in Thailand, was used as a prior model [3].

Results :

Pharmacokinetic model

- A 5-transit absorption compartment followed by 3-distribution compartment model was used to describes the observations according to the prior study [3].
- \$PRIOR** functionality was applied to stabilise the model estimation step.
- A conversion factor between the capillary and the venous dry-blood spot (DBS) concentrations was estimated (2.62, 95% CI: 2.35 – 2.87)
- Gestational age and other baseline covariates had no significant effect on the pharmacokinetic properties of piperaquine.
- The final PK model described the data adequately (**Fig. 1**).

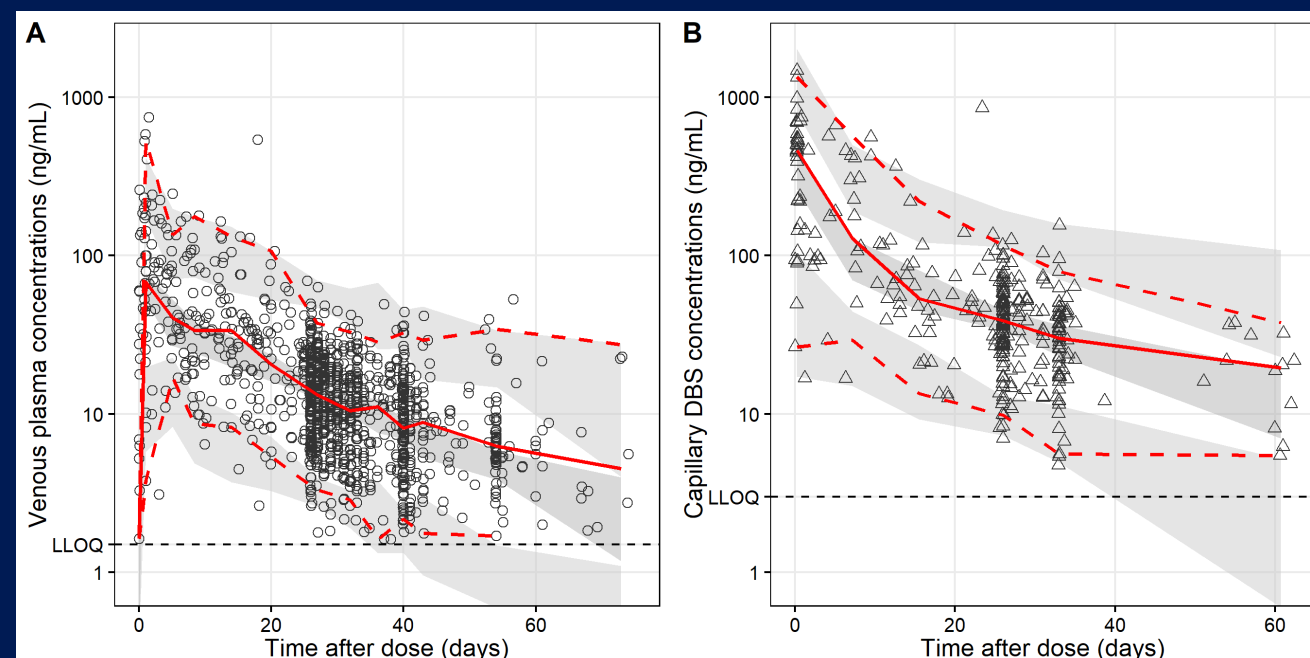


Figure 1 Visual predictive plots of piperaquine in pregnant women in Kenya (A) and Indonesia (B).

Conclusion :

- Population pharmacokinetic properties of piperaquine were successfully evaluated in pregnant women receiving IPTp.
- Modelling and simulation suggested that more than 90.3% of pregnant women who receive three monthly courses of IPTp achieved piperaquine exposures associated with protection against acquired malaria infections.
- Predicted peak concentrations did not accumulate with repeated dosing courses, suggesting that IPTp with DP is not likely to increase the risk for QT-prolongation associated with piperaquine treatment but further cardiac safety data is still needed.
- Translational simulations suggested that providing a full treatment dose of DP at monthly intervals provides sufficient protection to prevent malaria infection.
- Monthly administration of a DP has the potential to offer optimal prevention of malaria during pregnancy.**

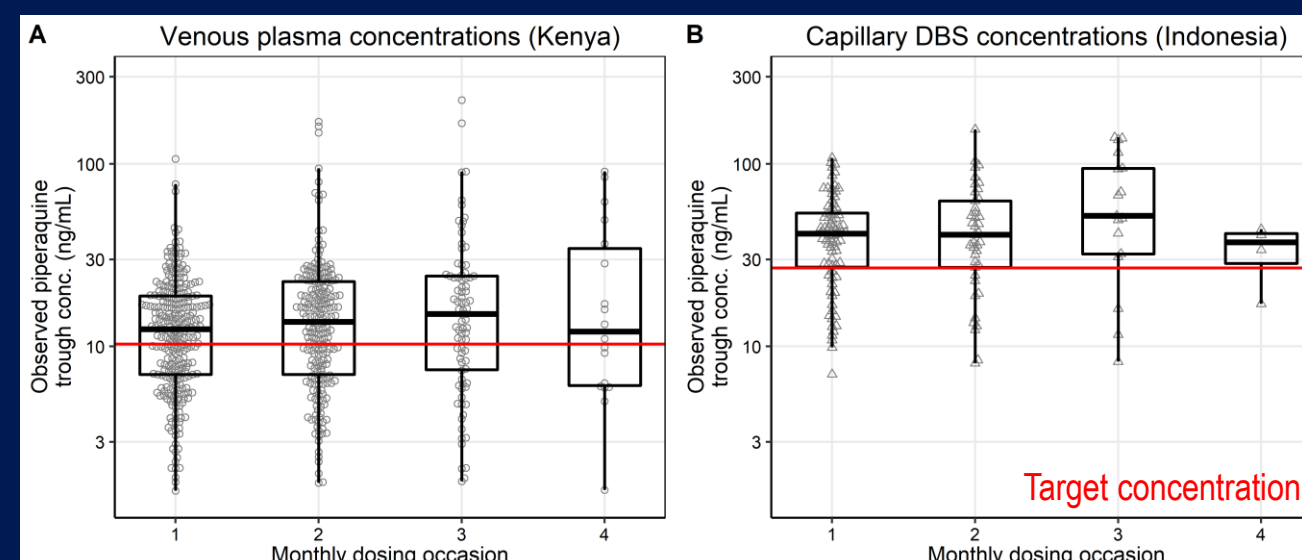


Figure 2 (A) Accumulation of plasma trough concentrations in Kenyan pregnant woman, and (B) capillary dry-blood spot (DBS) trough concentrations in Indonesian pregnant women.

Implication on placental malaria

- Placental malaria at delivery was accessed by either rapid diagnostic test, blood smear, placental blood PCR, or placental tissue histology.
- Placental malaria were detected in 3.3% (3/92) of Indonesian women and 31.7% (112/353) of Kenyan women
- In Kenyan women, only 0.9% (3/350) and 1.14 (4/350) had acute and chronic infections, respectively, the remaining were past infections.
- It was impossible to implement a pharmacodynamic model due to insufficient number of active placental malaria cases.

Interpretations

- Trough concentrations accumulated with each month of treatment and reached the target concentration of 10.3 ng/mL (**Fig. 2**).
- After three round of the monthly IPTp, less than 10% of individuals had trough concentrations below the target concentration (**Fig. 3B**).
- The piperaquine plasma concentrations became sub-therapeutic within one week prior to the next IPTp dose. New infections acquired within this window are unlikely to result in clinical symptoms since there is insufficient time for the malaria parasites to replicate to the level of symptomatic parasitaemia (**Fig. 3C**).

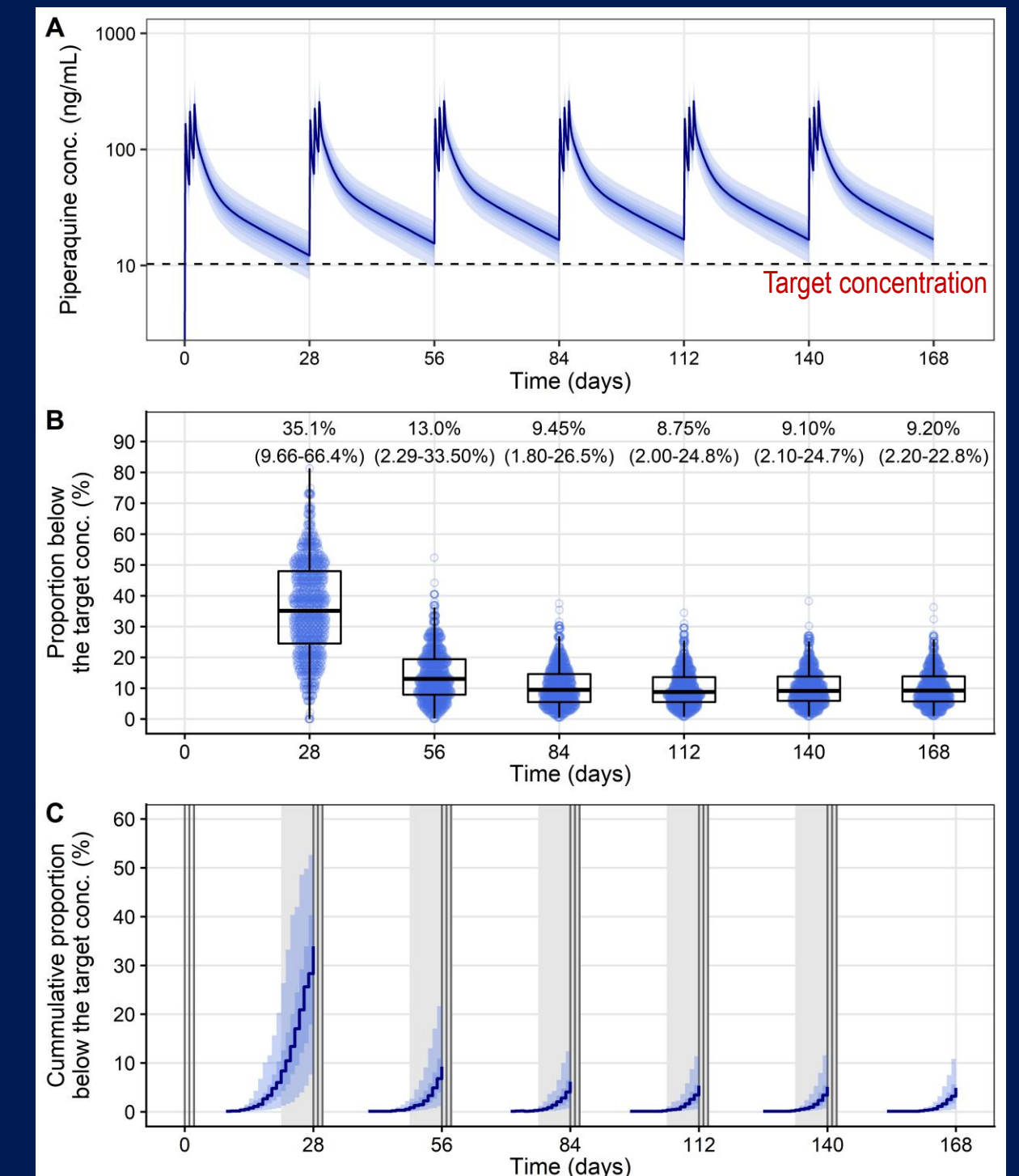


Figure 3 Simulation of monthly piperaquine dosing in pregnant women receiving IPTp. (A) Venous piperaquine plasma concentrations vs. time (n = 1000). (B) The proportion of patients with piperaquine trough concentrations below the target concentration of 10.3 ng/mL [4]. (C) The blue solid line represents the cumulative proportion of patients with plasma concentrations below the target concentrations.

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