OBJECTIVES

Develop a population pharmacokinetic (PK) model for PQ by pooling data from 5 studies and applying it to predict the PK of PQ in pediatric patients (6-12 months old) infected with Plasmodium falciparum malaria after the administration of a new dispersible formulation.

DATA

Tables 1 and 2 summarize the 5 studies used in the PK modeling of PQ used to predict the PK of PQ in pediatric patients suffering from Plasmodium falciparum malaria.

METHODS

Subjects/patients with at least one measurable PQ concentration were included in the analysis for a total of 207 PQ profiles and a variance equal to ($\sigma^2$).

RESULTS

A three-compartment model with lag-time, zero-order absorption (T0d), and enterohepatic circulation was the structural model that best fit the PQ data. Dose-corrected body weight improved the BIC. Inter-occasion variability (IOV) on the bioavailability parameter for the first dose improved the model. FED was a significant covariate on the relative bioavailability (Frel) in healthy subjects. Body weight, height, food, formulation, crushed, and sex were covariates included in the final model. Fixing the $\sigma$ to 0.01 improved the BIC as well as using a diagonal covariance matrix for the parameter versus a full matrix. The enterohepatic circulation was coded by estimating the time after the start of dose absorption when the gall bladder (Tgall) was emptying sending PQ back into the gastro intestinal (GI) track. It was assumed that the absorption from the gall bladder emptying was a zero-order absorption with the same k0 value as with the previous dose. The coding of the IOV and FED on the bioavailability was done directly on the administered dose, i.e. the dose was corrected in function of the FED status and the occasion. The coding of the different covariates on the mean of the PK parameter is presented below.

CONCLUSION

A three-compartment model with a lag-time, zero-order absorption, and enterohepatic circulation was the structural model that best fit the PQ data. Simulated results for the new dispersible formulation under fasted condition suggested that the geometric mean of PQ AUC and Cmax would be 11,322 ng/mL*h and 294 ng/mL, respectively, with a median Tmax of 5.48 h.

REFERENCES