Modeling and Simulation of Piperaquine (PQ) after Administration of Eurartesim® (PQ Tetraphosphate/Dihydroartemisinin)

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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.

Table 1: Summary of the Studies (Part I)

Study #	Health Status	Population	Sex	Race	Formulation	Crushed	Food	PQ Dose (mg)	Mean PQ Dose (mg/kg)
1	Patient	Pediatric	Male/Female	Black	Old	Yes	Fasted	160/320	18.7
2	Patient	Adult	Male	Asian	Old	No	Fasted	960	18.8
3	Healthy	Adult	Male/Female	Asian/Caucasian	Old	No	Fed	960/1280	16.2
4	Healthy	Adult	Male	Caucasian	Old	No	Fasted/Fed	1280	15.7
5	Healthy	Adult	Male	Black/Caucasian	Old/New	Old Yes/New No	Fasted	960	13.9

Table 2: Summary of the Studies (Part II)

Study #	n	Mean Age (year)	Mean Weight (kg)	# Male	# Female	# Asian	# Black	# Caucasian	# Fasted	# Fed	# Old	# New	# Samples	# Measurable Concentrations
1	30	2.70	11.3	15	15	0	30	0	30	0	30	0	114	97
2	25	26.7	51.4	25	0	25	0	0	25	0	25	0	424	375
3	79	24.8	64.9	51	28	26	0	53	0	79	79	0	2424	2369
4	37	25.6	81.9	37	0	0	0	37	19	18	37	0	702	681
5	36	33.4	69.1	36	0	0	13	23	36	0	18	18	972	900
Total	207	23.5	59.3	164	43	51	43	113	110	97	189	18	4636	4422

METHODS

Subjects/patients with at least one measurable PQ concentration were included in the analysis for a total of 207 PQ profiles and 4636 samples (4422 measurable samples). The maximum likelihood solution via the expectation-maximization algorithm (MLEM) in ADAPT 5[1], modeling software for population pharmacokinetic and pharmacodynamic systems analysis, was used to estimate the population parameters. The M3 method from Beal[2] was used for concentrations below the limit of quantification (BLQ). The PK parameters were assumed to be normally distributed. The residual error of the observed data was as follows: $Y_{observed} = Y_{predicted} + \varepsilon$, where ε was assumed to be normally distributed with a mean of zero and a variance equal to $(Y_{predicted} \times \sigma_{slope} + \sigma_{intercept})^2$. The covariates age, body weight (WGT), body surface area, sex (SEX), race, fasted/fed (FED), health status healthy/patient (PAT), formulation old/new (FORM), and crushed/not crushed (CRSH) were explored. Plots of the residuals of the parameter versus the covariate were used for covariate selection. The Bayesian Information Criteria (BIC) was used for model discrimination and covariate inclusion/exclusion. Internal model validation was done with visual predictive check plots created with R[3] version 3.1.2, a software environment for statistical computing and graphics.

RESULTS

A three-compartment model with lag-time, zero-order absorption (Tk0), 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, health status, food, formulation, crushed, and sex were covariates included in the final model. Fixing the $\sigma_{intercept}$ 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 administrated dose, i.e. the dose was corrected in function of the FED status and the occasion. The coding of the different covariate on the mean of the PK parameter is presented below.

$$Lag = Lag_{Base} \times (FED \times Lag_{FED} + 1 - FED) \times (CRSH \times Lag_{CRSH} + 1 - CRSH) \times (FORM \times Lag_{FORM} + 1 - FORM),$$

$$Tk0 = Tk0_{Base} \times (CRSH \times Tk0_{CRSH} + 1 - CRSH) \times (PAT \times Tk0_{PAT} + 1 - PAT),$$

$$CL/F = CL/F_{Base} \times (FED \times CL/F_{FED} + 1 - FED) + (WGT - 59.3) \times CL/F_{WGT},$$

$$CLdt/F = CLdt/F_{Base} \times (SEX \times CLdt/F_{SEX} + 1 - SEX),$$

where FED = 0 for fasted and 1 for fed, CRSH = 0 if the administrated dose was not crushed and 1 if it was crushed, FORM = 0 for the old formulation and 1 for the new formulation, PAT = 0 for healthy subject and 1 for patient, and SEX = 0 for male and 1 for female.

Table 3 lists the PQ population estimated PK parameters and their corresponding standard error as a percent of their corresponding maximum likelihood estimates (%RSE). Table 4 presents the diagonal of the covariance matrix (i.e. the variance) of the PK parameters. Figure 1 presents the goodness of fit plots for the final PQ model.

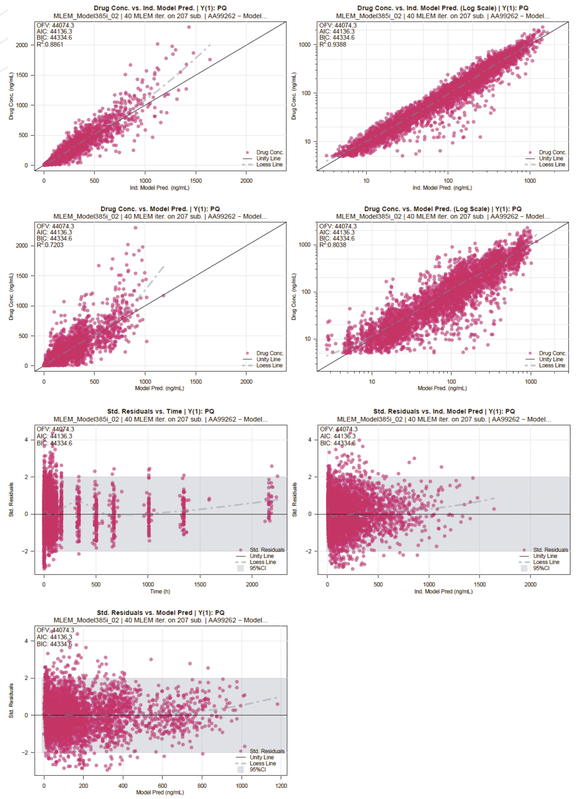
Table 3: Estimated PQ Population PK Parameters

Parameter	Estimate	%RSE
Lag (h)	0.758	2.90
Lag_{FED}	1.20	3.34
Lag_{CRSH}	0.287	16.0
Lag_{FORM}	0.460	7.26
$Tk0_{Base}$ (h)	2.83	4.28
$Tk0_{CRSH}$	0.705	18.6
$Tk0_{PAT}$	1.59	7.25
CL/F_{Base} (L/h/kg)	0.745	6.75
CL/F_{FED}	1.94	8.47
CL/F_{WGT} (L/h/kg/kg)	-0.00597	33.3
Vc/F (L/kg)	38.8	5.66
CLd/F (L/h/kg)	5.39	6.50
Vp/F (L/kg)	72.0	5.40
$CLdt/F_{Base}$ (L/h/kg)	1.81	4.79
$CLdt/F_{SEX}$	0.733	11.1
Vdt/F (L/kg)	861	5.82
Tgall (h)	1.49	8.88
$Frel_{FED}$	2.74	4.28
F_{OCC1}	0.867	4.63
σ_{slope}	0.322	1.03

Table 4: Population Estimate Variance of the PK Parameters

Parameter	Variance
Lag (h)	0.0127
Tk0 (h)	0.840
CL/F (L/h/kg)	0.0637
Vc/F (L/kg)	194
CLd/F (L/h/kg)	3.48
Vp/F (L/kg)	411
CLdt/F (L/h/kg)	0.321
Vdt/F (L/kg)	129000
Tgall (h)	0.0778
$Frel_{FED}$	0.132
F_{OCC1}	0.113

Figure 1: Goodness of Fit Plots



Plots created using the R AMGET package [5]

Internal validation was performed with visual predictive check (VPC) with 100 simulations for each profile/observed concentrations. Each BLQ measured or simulated was set to 2.5 ng/mL (half the lower limit of quantification of 5 ng/mL). The VPC plots on the log-log scale with data and without data are presented in Figures 2 and 3.

Figure 2: Visual Predictive Check Plot (with Data)

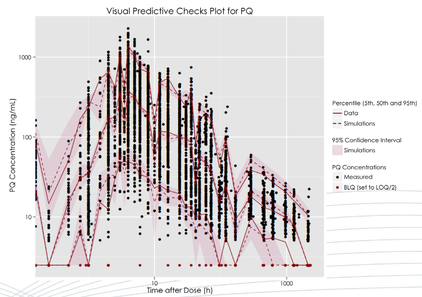
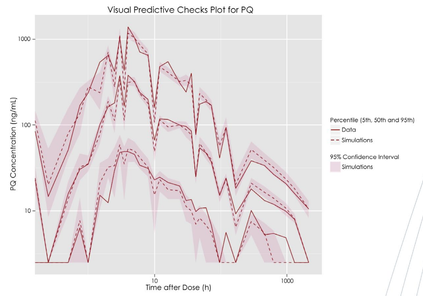
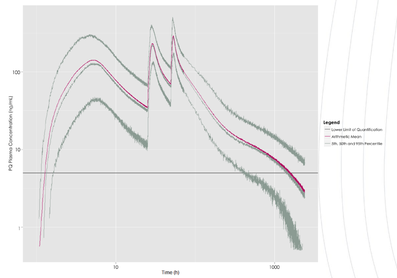


Figure 3: Visual Predictive Check Plot (without Data)



Two hundred (200) infants (gender balanced) were simulated receiving 80, 160, or 320 mg PQ, depending on their WGT, once a day for 3 consecutive days under fasted condition. WGT was simulated according to the WHO training[4]. Day 3 AUC, Cmax and Tmax were calculated. Figure 4 displays the percentiles (5th, 50th, and 95th) and the mean of the simulated PQ concentrations for the new treatment with output noise under fasted.

Figure 4: Simulated PQ Concentrations for 200 Infants (6-12 Months Old) Patients under Fasted Condition



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 suggest 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.

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