Modeling and Simulation of Smear Count after Administration of Eurartesim® (piperaquine (PQ) tetraphosphate/dihydroartemisinin (DHA)) in Infected Patients with *Plasmodium falciparum* Malaria

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Objectives

Develop a population pharmacokinetic and pharmacodynamic (PK/PD) model for the treatment and smear count of *Plasmodium falciparum* by pooling data from 5 studies (PK part), 2 patient studies (PD part), and applying them to predict the smear count in pediatric patients (6-12 months) infected with *P. falciparum* malaria following the administration of a new dispersible formulation.

PD Data

- **Study #1:** Phase I/II, open-label, PK, safety, and efficacy study on Eurartekin™ tablets [(20 mg DHA/160 mg PQ], in pediatric patients with *P. falciparum* malaria in Africa (Burkina Faso). A total of 32 patients (16 males and 16 females) were dosed. The tablet was crushed, mixed with water, and administered as a 120 mL slurry. Three (3) doses were administrated over 3 consecutive days at 24-hour intervals (once a day on Visits 1, 2, and 3). The number of tablets administered was based on patient body weight: 1 pediatric tablet for 7 < 13 kg and 2 pediatric tablets for 13 < 24 kg body weight. On the first day of treatment the dose was administered between 1-18 hours following last food intake (median 4.5 hours). A drop of blood was collected on Days 0-4, 7, 14, 21 (+7), 28 (±7), 42, and 90 (±7).

- **Study #2:** Phase I/II, open-label, PK, safety, and efficacy study on Artekin™ tablets (40 mg DHA/320 mg PQ), in adult patients with *P. falciparum* malaria in Thailand. Data from 25 male patients were used in the PD analysis. Three (3) doses were administrated over 3 consecutive days at 24-hour intervals (3 tablets once a day based on body weight, all patients were < 75 kg). On 3 days of treatment the dose was administered 3-6 hours following the last intake of food (median 4.5 hours). A drop of blood was collected on Days 0 - 3, 7, 14, 21, 28 (+7), 56 (±7), and 90 (±7).

Thick and thin blood smears were obtained from the patient to verify the presence of *P. falciparum* and to calculate the asexual and sexual parasite densities. Blood smear assessment was performed twice a day from a drop of blood until the test results came back negative for asexual forms of the parasite.

Tables 1 and 2 summarize the 2 studies used in the PD modeling for predicting the parasite count in pediatric patients suffering from *P. falciparum* malaria.

Table 1. Summary of the Studies (Part I)

Study	Population	Sex	Race	Crushed	Food	DHA / PQ Dose (mg)	Mean DHA / PQ Dose (mg/kg)
1	Pediatric	Male/Female	Black	Yes	Fasted	20&40/160&320	2.34/18.7
2	Adult	Male	Asian	No	Fasted	120/960	2.35/18.8

Table 2. Summary of the Studies (Part II)

Study	n	Mean Age (year)	Mean Weight (kg)	Number of Male	Number of Female	Number of Asian	Number of Black	Number of Fasted	Number of Samples	Number of Positive Smears
1	25	2.68	11.3	11	14	0	25	25	239	38
2	25	26.7	51.4	25	0	25	0	25	307	108
Total	50	14.7	31.3	36	14	25	25	50	546	146

Methods

PK parameters for both drugs were developed[1,2] and the Bayesian estimates were fixed. The patients with Bayesian estimated PK parameters from both medications were included in the analysis for a total of 50 smear count profiles, 546 samples (146 greater than zero). The MLEM algorithm in ADAPT5[3] was used to estimate the population PD parameters. The natural logarithm of the smear count plus two was used for PD modeling. The initial conditions were fixed to the measure smear level before administration of the medication. The covariates age, body weight (WGT), body surface area, sex, race (RACE), fasted/fed, and crushed/not crushed were explored. The Bayesian Information Criteria (BIC) was used for model discrimination and covariate inclusion/exclusion.

Results

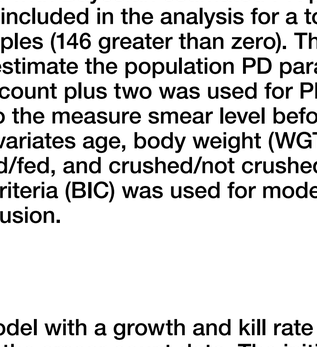
A one-compartment model with a growth and kill rate based on both medications best fitted the smear count data. The initial conditions were fixed to the observed parasite count and the predicted values for the model were the logarithm of the predicted parasite count plus two. An antagonistic effect was assumed between the 2 medications[4], i.e., less than additive effect, the worst case scenario was assumed by taking the killing rate to be the maximum effect for the 2 medications. DHA and PQ effects were modeled with an Emax and a sigmoidal Emax model, respectively. An onset of effect parameter was added to model the delay on the PD effect compared to the PK concentrations and the inclusion of RACE on DHAmax, both which improved the BIC. It was suspected that RACE was more a marker of different parasite populations since 1 study was conducted in Asia on Asian adult patients while the other study was conducted in Africa on Black pediatric patients. The covariate RACE as well as the killing rate was coded in the ADAPT5 as follows:

$$DHAmax = DHAmax_{Asian} \times (1\text{-}RACE) + DHAmax_{Black} \times RACE;$$

$$K_{kill} = Max(DHAmax * C_{DHA}/(DHA50 + C_{DHA}),\ PQmax \times C_{PQ}^{HillPQ}/(PQ50^{HillPQ} + C_{PQ}^{HillPQ}));$$

where DHAmax and PQmax were the maximum killing rates for DHA and PQ, respectively, RACE = 0 for Asians and 1 for Blacks. K_{kill} was the parasite killing rate, C_{DHA} and C_{PQ} were the DHA and PQ concentrations, respectively. DHA50 and PQ50 were the concentrations of DHA and PQ with 50% of the maximum killing rate, respectively, and HillPQ was the hill parameter for the sigmoidal Emax model for PQ. The graphic representation of the parasite count model can be found in Figure 1.

Figure 1. Parasite Count Model



The variance of the PD model was $Var(Y_{pred}) = (\sigma_{slope} \times Y_{pred} + \sigma_{inter})^2$ where σ_{slope} and σ_{inter} were the proportional and additive terms of the error model, respectively, and Y_{pred} was the predicted log(parasite count + 2). Table 3 lists the population estimated PD parameters and their corresponding standard error as a percent of their corresponding maximum likelihood estimates (%RSE). Table 4 lists the standard deviation and the corresponding %RSE for the parameters in the final model. Figure 2 displays the goodness of fit plots for the final parasite model.

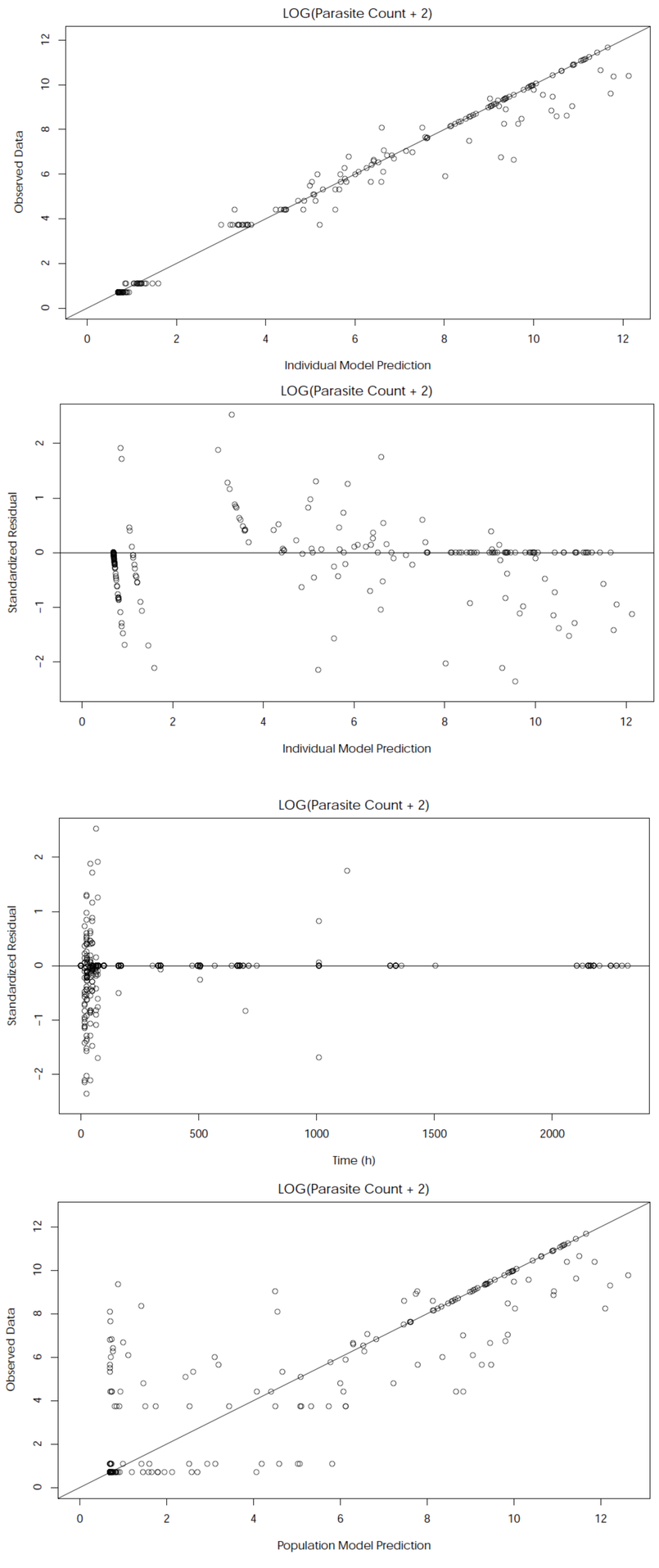
Table 3. Estimated Parasite Population Parameters

Parameter	Mean	%RSE
Kgrow (1/h)	0.0606	1.98
$DHAmax_{Asian}$ (1/h)	0.530	9.55
$DHAmax_{Black}$ (1/h)	1.13	14.6
DHA50 (ng/mL)	0.200	28.2
PQmax (1/h)	0.209	24.6
PQ50 (ng/mL)	19.6	4.37
HillPQ	15.5	21.4
OnSet (h)	9.75	17.3
σ_{slope}	0.128	13.7
σ_{inter}	0.0274	48.1

Table 4. Standard Deviation and %RSE for the PK Parameters in the Final Model

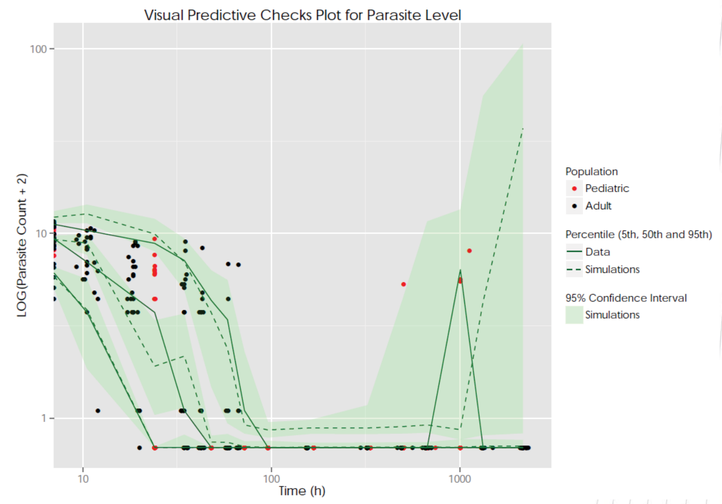
Parameter	Std.Dev.	%RSE
Kgrow (1/h)	0.000226	202
DHAmax (1/h)	0.171	20.4
DHA50 (ng/mL)	0.0222	126
PQmax (1/h)	0.103	51.7
PQ50 (ng/mL)	0.299	177
HillPQ	1.20	403
OnSet (h)	5.49	26.8

Figure 2. Goodness of Fit Plots



Internal validation was performed with the use of a visual predictive check (VPC) plot with 1000 simulations for each profile/observed concentration. Each simulated log(parasite count + 2) lower than log(2) was replaced to log(2) (since the parasite count cannot be negative). The VPC plot of the log(parasite count + 2) is presented in Figure 3.

Figure 3. Visual Predictive Check Plot



The model estimated a 48-hour parasite growth rate in blood to be 18.3 fold, which was within the range reported in the literature [5]. For the simulations, WGT was simulated according to the WHO training [6]. One thousand Black infants were simulated receiving 80/10, 160/20, or 320/40 mg PQ/DHA depending on their WGT with medication administered once a day for 3 consecutive days. Each of the simulated patients was simulated 3000 times with output noise and the mean of the concentration was used at each time point. Twenty-one virtual patients did not produce output files with values, hence they were not included in the analysis. The simulated results suggested a geometric mean parasite clearance time of 22.5 hours (range 10 - 65 hours).

Figures 4 and 5 present the arithmetic and geometric mean as well as the 5th, 50th (median), 95th percentile of the simulated LOG(parasite count + 2) and parasite count following the administration of the first dose.

Figure 4. LOG(Parasite Count + 2) for Simulated Infants (6-12 Months) Patients under Fasted Condition

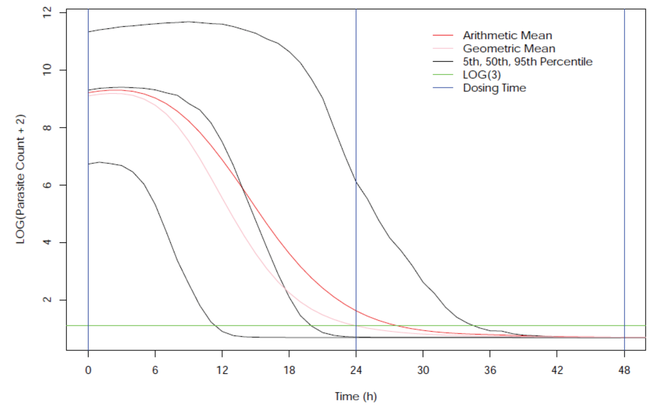
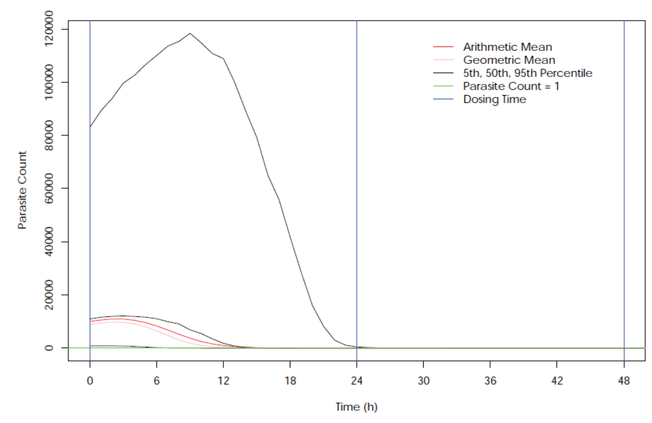


Figure 5. Parasite Count for Simulated Infants (6-12 Months) Patients under Fasted Condition



Conclusion

The model described well the parasite smear level count and the geometric mean parasite clearance time of 22.5 hours.

References

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