Modeling and simulation of dihydroartemisinin (DHA) after administration of Eurartesim® (piperaquine tetraphosphate/DHA)

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OBJECTIVE

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

DATA

Study #1: Phase I/II, open-label, PK, safety, and efficacy study on Eurartekin® tablets [20 mg DHA/160 mg piperaquine tetraphosphate (PQP)], 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 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). PK blood samples for DHA were sparse with 1 or 2 samples per patient collected at the following times: pre-dose, 1.5, 3, 6, and 12 hours following the first dose.

Study #2: Phase I/II, open-label, PK, safety, and efficacy study on Artekin™ tablets (40 mg DHA/320 mg PQP), in adult patients with *P. falciparum* malaria in Thailand. Data from 25 male patients were used in the PK analysis. Three 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 the 3 days of treatment the dose was administered 3 - 6 hours following the last intake of food (median 4.5 hours). Blood sampling for PK analysis of DHA in plasma were collected at pre-dose (within 1 hour prior to the first drug administration) and at the following times: 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours post first dose.

Study #3: Phase I, PK study, in healthy male and female adult Asian and Caucasian participants to investigate the PK profiles of Eurartesim tablets (40 mg DHA/320 mg PQP). Eurartesim tablets were administered orally under fed conditions, following a light continental breakfast (approximately 359 kcal) for 3 consecutive days (Days 0, 1, and 2). The dose administered was based on body weight (3 tablets/day for body weight < 75 kg and 4 tablets/day for body weight ≥ 75 kg). Seventy-eight (78) participants were included in the PK analysis for DHA. Blood samples for determination of plasma DHA were collected at the following times: pre-dose on Day 0 and Day 2 and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours post-dose following drug administration on Day 0 and Day 2.

Study #4: Phase I, randomized, open-label, balanced, single-dose, 2-treatment (fed and fasted conditions) parallel design study conducted in healthy male participants. The study population consisted of healthy Caucasian males, age ranging between 18 - 50 years, BMI ranging between 19 - 27 kg/m^2 and body weight ≥ 75 kg. The PK of DHA following a single oral dose of Eurartesim tablets (40 mg DHA/320 mg PQP) was assessed. All participants dosed in this study were administered 4 tablets. A single oral dose was administered with 200 mL of water on the morning of Day 0, following an overnight fast of at least 10 hours (fasted group) or following a standardized high fat and high caloric breakfast (50% fat and 800 - 1000 kcal), which started 30 minutes prior to drug administration (fed group). During the study, blood samples were collected from each participant for DHA PK assessment at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours post-dose. Thirty-six (36) participants were planned for the study (18 in each group). However, 37 participants received a dose and were included in the PK analysis of DHA.

Study #5: Phase I, open-label, randomized, balanced single-dose, 2-treatment, parallel groups study. This relative bioavailability study was to assess the PK of DHA of a new Eurartesim dispersible formulation versus the crushed marketed Eurartesim film coated formulation following oral administration in healthy male participants. A total of 36 healthy adult male participants with body weight < 75 kg (2 groups of 18 participants) were enrolled. Each Eurartesim formulation (dispersible tablet or film coated tablet to be crushed) contained 20 mg DHA/160 mg PQP. All participants were dosed orally with 6 Eurartesim film coated crushed tablets or 6 Eurartesim dispersible tablet formulation for a total dose of 180 mg DHA/960 mg PQP (corresponding to 3 adult tablets for body weight < 75 kg), in accordance to the following dose regimen: Group 1: On Day 1, the participants received 6 tablets of the Eurartesim dispersible formulation (New) dispersed in 60 mL of non-carbonated water. After ingestion, another 40 mL of non-carbonated water was added to the beaker for rinsing and consumed by the participant. Group 2: On Day 1, the participants received 6 tablets of the Eurartesim film coated formulation (Old Crushed) mixed within 60 mL of non-carbonated water. After ingestion, another 40 mL of non-carbonated water was added to the beaker for rinsing and consumed by the participant. The dose was administrated 3 hours after a standard light breakfast and no food was allowed for at least 3 hours after. During the study, blood samples were collected for the PK assessment of DHA at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 hours post-dose.

Tables 1 and 2 summarizes the 5 studies used in the PK modeling of DHA used to predict the PK of DHA in pediatric patients suffering from *P. falciparum* malaria.

Table 1: Summary of the Studies (Part I)

Study #	Health	Population	Sex	Race	Formulation	Crushed	Food	DHA Dose (mg)	Mean DHA Dose (mg/kg)
1	Patient	Pediatric	Male/Female	Black	Old	Yes	Fasted	20/40	2.34
2	Patient	Adult	Male	Asian	Old	No	Fasted	120	2.35
3	Healthy	Adult	Male/Female	Asian/Caucasian	Old	No	Fed	120/160	2.01
4	Healthy	Adult	Male	Caucasian	Old	No	Fasted/Fed	160	1.96
5	Healthy	Adult	Male	Black/Caucasian	Old/New	Old Yes/New No	Fasted	120	1.74

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	25	2.68	11.2	11	14	0	25	0	25	0	25	0	43	26
2	25	26.7	51.4	25	0	25	0	0	25	0	25	0	375	236
3	78	24.9	65.1	51	27	26	0	52	0	78	78	0	1932	1319
4	37	25.6	81.9	37	0	0	0	37	19	18	37	0	481	348
5	36	33.4	69.1	36	0	0	13	23	36	0	18	18	576	390
Total	201	24.0	60.5	160	41	51	38	112	105	96	183	18	3407	2319

METHODS

Participants/patients with at least one measurable DHA concentration were included in the analysis for a total of 201 DHA profiles, 3407 samples (2319 were measurable). The MLEM algorithm in ADAPT5[1] was used to estimate the population parameters. Concentrations below the limit of quantification (BLQ) were treated as censored. The M3 method from Beal[2] was used. The PK parameters were assumed to be normally distributed. The residual error of the observed data was as follow: $Y_{observed} = Y_{predicted} + \varepsilon$, 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, race, fasted/fed (FED), health status healthy/patient (PAT), formulation old/new (FORM) and crushed/not crushed were explored. The general additive model in R[3] Version 3.0.1 was used for covariate selection. The Bayesian Information Criteria (BIC) was used for model discrimination and covariate inclusion/exclusion.

RESULTS

A one-compartment model with a lag time and a zero-order absorption was the structural model that best described the DHA data. Body weight corrected dose improved the BIC. PAT was a significant covariate on Lag, zero-order duration (Tk0), and relative bioavailability (Frel) (on healthy). FED was a significant covariate on Lag and Tk0. FORM was a significant covariate on Frel (on the old formulation). The coding of the different covariate on the mean of PK parameter is presented below.

$Lag = Lag_{Healthy_and_Fasted}$ if Healthy Participant and Fasted, else $Lag = Lag_{Patient_or_Fed}$,

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

$Frel = (PAT \times Frel_{PAT} + 1 - PAT) \times (FORM \times Frel_{FORM} + 1 - FORM)$,

$CL/F = CL/F_{Base}/Frel$,

$Vc/F = Vc/F_{Base}/Frel$,

where PAT = 0 if healthy participant and 1 if patient, FED = 0 if fasted and 1 if fed, and FORM = 0 if old formulation and 1 if new formulation.

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

Table 3: Estimated DHA Population PK Parameters

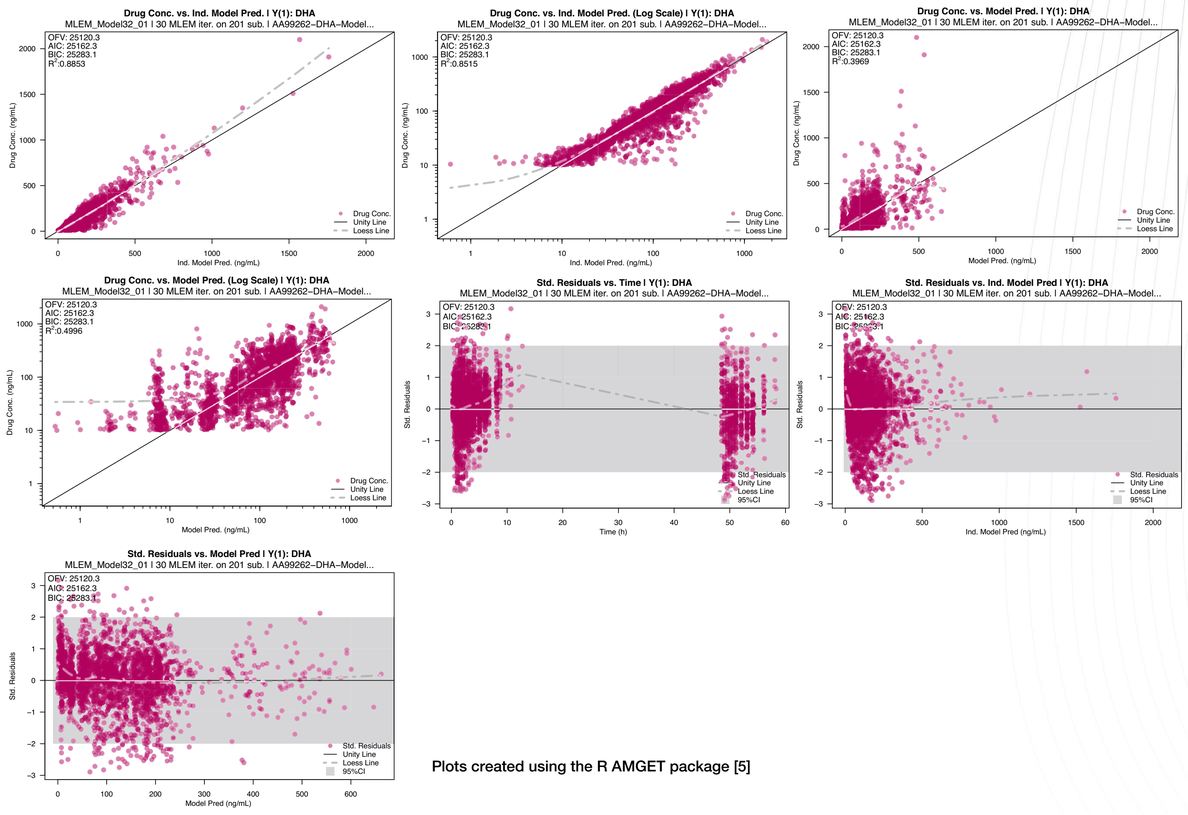
Parameter	Estimate	%RSE
$Lag_{Healthy_and_Fasted}$ (h)	0.204	40.8
$Lag_{Patient_or_Fed}$ (h)	2.25	3.71
$Tk0_{Base}$ (h)	1.04	8.02
$Tk0_{PAT}$	1.91	4.35
$Tk0_{FED}$	2.33	3.57
CL/F_{Base} (L/h/kg)	3.08	2.70
Vc/F_{Base} (L/kg)	4.74	1.76
$Frel_{PAT}$	2.03	4.10
$Frel_{FORM}$	0.715	11.6
σ_{slope}	0.305	1.40
$\sigma_{intercept}$	3.29	0.130

Table 4: Lower-Diagonal of the Covariance Matrix

	Lag (h)	Tk0 (h)	CL/F (L/h/kg)	Vc/F (L/kg)
Lag (h)	0.0701			
Tk0 (h)	0.0567	0.903		
CL/F (L/h/kg)	0.0616	0.162	0.950	
Vc/F (L/kg)	0.0702	0.181	1.15	1.83

Figure 1

Goodness of Fit Plots

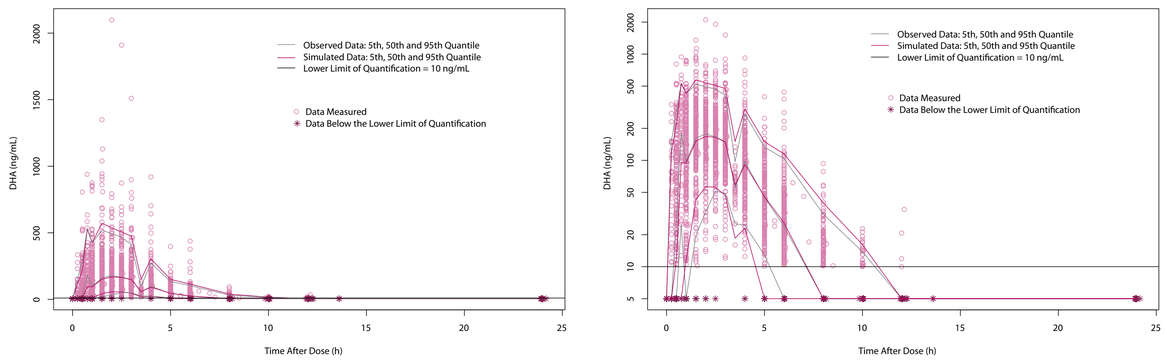


Plots created using the R AMGET package [5]

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 5 ng/mL (half the lower limit of quantification of 10 ng/mL). The VPC on the original scale and semi-log plot are presented in Figure 2.

Figure 2

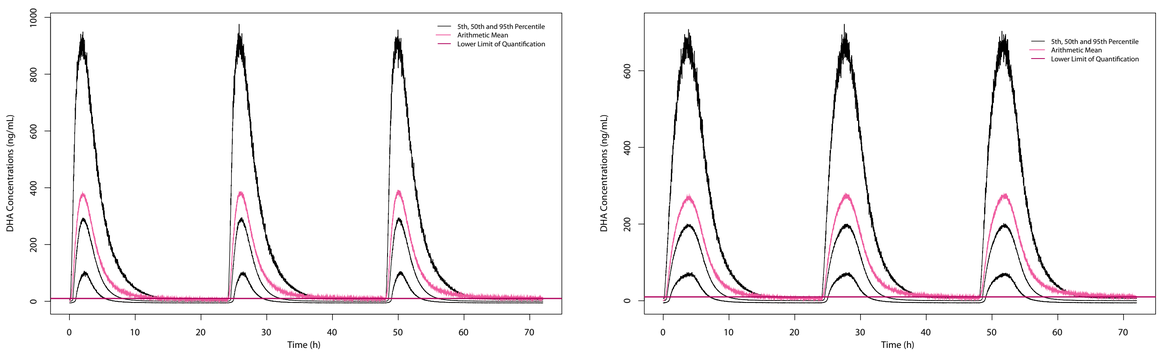
Visual Predictive Check Plot (Linear Scale) **Visual Predictive Check Plot (Semi-Log Scale)**



Two thousand infants were simulated (gender balanced) receiving 10, 20, or 40 mg of DHA depending on their WGT (< 7 kg, 7 to < 13 kg and ≥ 13 kg, respectively) once a day for 3 consecutive days. The body weight were simulated according to the WHO training[4] and AUC, C_{max} and T_{max} values were estimated. Figure 3 displays the percentiles (5th, 50th and 95th) and the mean of the simulated DHA concentrations for the new treatment with output noise under fasted and fed condition, respectively.

Figure 3

Simulated DHA Concentrations for 2000 Infants (6-12 Months Old) Patients under Fasted Condition **Simulated DHA Concentration for 2000 Infants (6-12 Months Old) Patients under Fed Conditions**



For the new dispersible formulation, the simulated results suggest that the geometric mean of DHA AUC (Dose/Clearance) and Day 3 C_{max} is approximately 1160 ng/mL*h and 407 ng/mL, respectively, under fasting condition and 1180 ng/mL*h and 237 ng/mL, respectively, under fed condition. The median Day 3 T_{max} is approximately 2.5 hours and 5.1 hours under fasting and fed condition, respectively.

CONCLUSION

A one-compartment structural model with a lag time and a zero-order absorption best described the PK of DHA. Body weight, health status, food and formulation were the 4 covariates which improved the model. It is expected that DHA will have similar exposure (AUC) under fasting and fed conditions; however, C_{max} under fed condition would be about half of that under fasting condition and T_{max} would bedelayed about 2.6 hours under fed relative to fasting condition.

REFERENCES

[1] D'Argenio, D.Z., A. Schumitzky and X. Wang. ADAPT 5 User's Guide: Pharmacokinetic/Pharmacodynamic Systems Analysis Software. Biomedical Simulations Resource, Los Angeles, 2009.

[2] Beal SL. Ways to fit a PK model with some data below the quantification limit. Journal of Pharmacokinetics & Pharmacodynamics. 2001;28(5):481-504.

[3] The R Project for Statistical Computing, R Manuals. http://www.r-project.org/

[4] Training Course on Child Growth Assessment – WHO – Module C: Interpreting Growth Indicators. http://www.who.int/childgrowth/training/module_c_interpreting_indicators.pdf

[5] Guiastrennec B, Wollenberg L, Forrest A and Ait-Oudhia S. AMGET, an R-Based Postprocessing Tool for ADAPT 5. CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e61.

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