Population pharmacokinetic and time-to-event modelling of the antimalarial drug lumefantrine in young children with severe acute malnutrition

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Objective & Methods

Objectives: This study aimed to characterise the pharmacokinetic-pharmacodynamic properties of the antimalarial lumefantrine in children with severe acute malnutrition (SAM).

Methods: 131 SAM children and 266 non-SAM children with uncomplicated *falciparum* malaria were administered with lumefantrine every 12 hours for 3 days. Malnutrition status was characterised using standard WHO guidelines [1]. Dry blood spot capillary concentrations were measured using LC-MS/MS. Nonlinear mixed-effects modelling was performed to characterise the pharmacokinetic properties of lumefantrine. Parasitemia at the time of recurrent infection was used to determine the possible starting interval of the malaria erythrocytic stage [2]. Then, an interval-censoring time-to-event model was used to describe the events (re-infections).

Conclusions

- **The PK/PD properties of lumefantrine were characterized accurately.**
  - *Pharmacokinetic model*: Two-transit absorption model followed by two disposition compartments. Allometric scaling of body weight and enzyme maturation effects were included into the model.
  - *Pharmacodynamic model*: Interval censoring time-to-event model.
- **SAM children have a lower lumefantrine exposure than normal children.**
- **Bioavailability was reduced by 25% per cm reduction in mid-upper arm circumference.**
- **The time-to-event model could accurately predict the starting interval of the malaria erythrocytic stage.**
- **Lumefantrine dose adjustment is needed urgently in SAM children.**

Results

Pharmacokinetic model

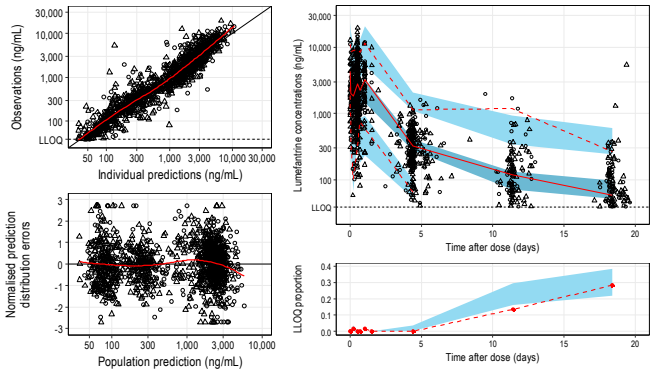


Figure 1. Final model GOF diagnostics.

- LLOQ data were modelled using the M6 method [3].
- Malnutrition associated covariates are highly correlated.
- Allometric function of body weigh and enzyme maturation effects were added into the pharmacokinetic model as priori knowledge.
- Covariate evaluation was performed using stepwise covariate modelling and full covariate approach.
- The MUAC was the most significant covariate on the bioavailability.

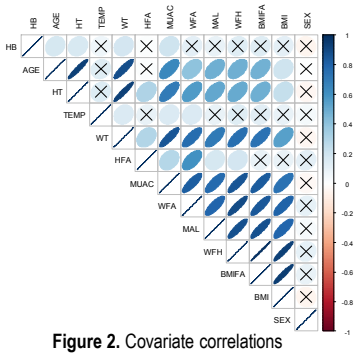


Figure 2. Covariate correlations

Effect of malnutrition status

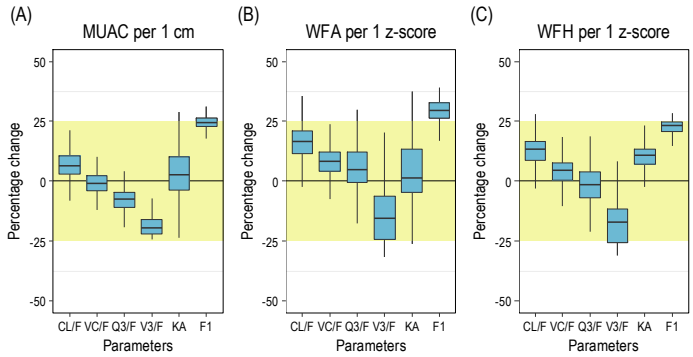
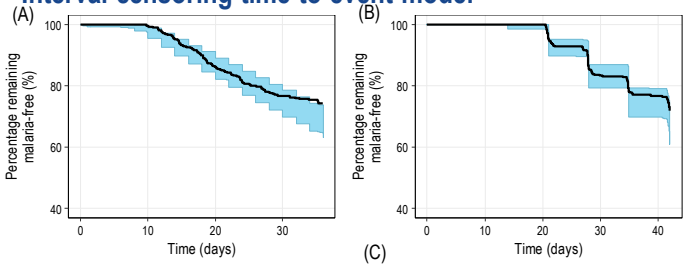


Figure 3. Full covariate approach (1,000 bootstraps). (A) Mid-upper arm circumference (MUAC), (B) weight for age z-score (WFA), and (C) weight for height z-score (WFH). The shaded areas represent a covariate effect of ±25%, assumed to be clinically insignificant.

Final parameter estimates

	Population estimates (%RSE)	95% CI of estimates	%CV of BSV (%RSE)	95% CI for BSV
Pharmacokinetic parameters				
F (%)	100% Fixed	-	62.7%	(51.0% - 72.6%)
MTT (h)	3.15 (19.4%)	1.94 – 4.33	100%	(73.4% - 136%)
CL/F (L/h)	2.65 (7.97%)	2.27 – 3.10	-	-
V_c/F (L)	117 (5.63%)	104 – 130	-	-
Q_p/F (L/h)	1.16 (12.6%)	0.896 – 1.45	62.8%	(51.5% - 74.8%)
V_p/F (L)	901 (24.9%)	504 – 1390	-	-
σ	0.351 (10.7%)	0.284 – 0.428	-	-
Covariates				
TM_{50} (months)	4.29 (31.1%)	2.06 – 7.38	-	-
HILL	1 Fixed	-	-	-
MUAC on F (% per 1 cm)	24.7% (9.06%)	20.5% – 29.8%	-	-
Pharmacodynamic parameters				
BASE (infections per years)	6.88 (12.3%)	4.62 – 7.30	-	-
IC_{50} (ng/mL)	149 (16.6%)	135 – 213	-	-
γ	4.68 (14.3%)	3.12 – 6.08	-	-

Interval-censoring time-to-event model



Hazard function:

$$Hz(t) = \Theta_{BASE} \times \left[1 - \frac{E_{MAX} \times CP^{\gamma}}{IC_{50}^{\gamma} + CP^{\gamma}}\right]$$

Survival function:

$$S(t) = \exp\left(\int_0^t Hz(t)dt\right)$$

Blood stage parasite interval:

$$I_{START} = \frac{1}{K_{growth}} \times \ln\left(\frac{PAR_{obs}}{10^4}\right)$$

$$I_{END} = \frac{1}{K_{growth}} \times \ln\left(\frac{PAR_{obs}}{10^5}\right)$$

Probability of an event occurring within interval:

$$P(a < t < b \mid \Theta) = 1 - [S(I_{START}) - S(I_{END})]$$

Probability of no-event during follow-up:

$$P(t > T \mid \Theta) = S(T)$$

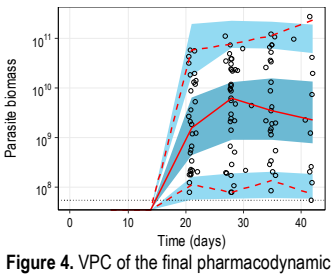


Figure 4. VPC of the final pharmacodynamic model: (A) time-to-blood stage infection, (B) time-to-malaria detection, and (C) predicted parasitemia.

DISCUSSIONS

Pharmacokinetic model:

- The observed data was best described by a two-compartment transit-absorption model followed by a three-compartment distribution model. The final pharmacokinetic model was robust and accurate according to internal and external model evaluation.
- Malnutrition status affect lumefantrine absorption significantly, i.e. the bioavailability increased by 25% per cm increase of MUAC.
- Lumefantrine dose adjustment is needed urgently in SAM children.

Interval-censoring time-to-event model:

- Modelling of the starting interval of the parasite blood stage [2] was robust and accurate. Lumefantrine concentrations showed a sigmoid E_{MAX} relationship with the baseline hazard of acquiring malaria.
- Final PKPD model described the time to malaria detection and the detected parasite biomass accurately.

References:

[1] World Health Organization (2009), WHO child growth standards and the identification of severe acute malnutrition in infants and children.

[2] Bergstrand, M., F. Nosten, K. M. Lwin, M. O. Karlsson, N. J. White and J. Tarning (2014). "Characterization of an in vivo concentration-effect relationship for piperaquine in malaria chemoprevention." Sci Transl Med 6(260): 260ra147.

[3] Ahn, J.E., et al., Likelihood based approaches to handling data below the quantification limit using NONMEM VI. J Pharmacokinet Pharmacodyn, 2008. 35(4): p. 401-21.

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