Lumenfantrine Exposure in Malnourished Children: PBPK modeling applied for Predictions and Dose Adjustments

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Objectives

- To develop a whole body PBPK model describing disposition of lumefantrine for predictions and assessments of drug exposure in malnourished children
- Perform retrospective risk-assessments and suggestion of adjustments to lumefantrine dosing in malnourished children.

Background

- Artemether-lumefantrine combination therapy accounted for 73 % of artemisinin-based combination therapies (ACT) for uncomplicated Plasmodium falciparum malaria in 2013 [1].
- The area under the blood or plasma concentration-time curve (AUC) and the concentration on day 7 of the slowly eliminated ACT, i.e., lumefantrine, components are considered important predictors of treatment outcome [2].

Methods

- A lumefantrine PBPK model was developed in PK-Sim® (v8) informed on physico-chemical, biopharmaceutical, and ADME properties using a middle out strategy to describe clinical observations on effects of food intake and CYP3A4 inhibition [3].

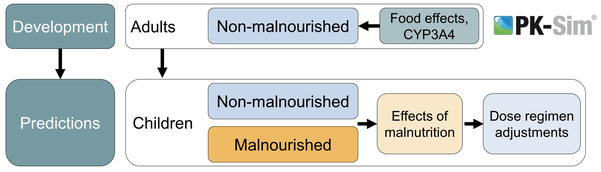

Figure 1. *Schematic overview of project: lumefantrine model development using a middle-out strategy in adults, pediatric population generation at non-malnourished and malnourished states and subsequent predictions for verification and dose investigations.*

- Intestinal absorption was informed from clinical food-effect studies and previous assessments of fraction absorbed (f_{abs}) in fasted and fed state [4, 5].
- Physiologically based translation from healthy adults to pediatric populations (non-malnourished and severely malnourished) was achieved using reported strategy and the simulated results were assessed towards clinical data [6].
- Dose adjustments for malnourished children was performed using simulated measures for non-malnourished children as therapeutic target reference.

Results

- The final lumefantrine model was described by logP=3.09, fu.p = 0.0029 and elimination via CYP3A4 ($Cl_{spec.}$=0.87 l/µmol/min) adopting the standard PK-Sim® calculation method for Kp values and cellular permeabilities. The plasma binding entity of lumefantrine was modelled using albumin as a surrogate to high-density lipoproteins. Intraluminal solubility, at fasted (9.7 µg/ml) and fed state (180 µg/ml), were estimated as a categorical effect along with prandial state specific dissolution, described by Weibull functions. The model was able to capture the reported increase in exposure after concomitant administration of the CYP3A4 inhibitor ketoconazole [7]. Model performance is visualized in Figure 1.

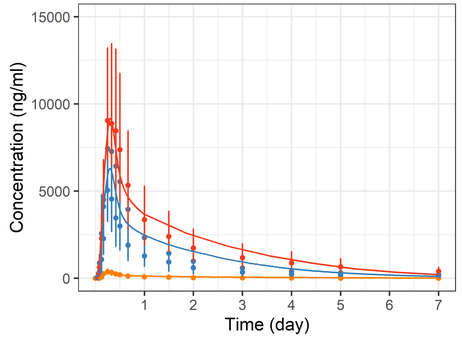

Figure 2. *Concentration-time profiles visualizing lumefantrine PBPK model performance. Lumefantrine plasma concentration-time profiles in adults after 480 mg oral dosing, at fasted state (orange), fed state (blue) and fed state with concomitant administration of the CYP3A4 inhibitor ketoconazole (red). Clinical observations are represented by dots (mean ± SD) while the solid lines represent simulations for a typical adult individual.*

- Pediatric simulations were performed assuming that the in-vivo effect of a nutritional drink on intraluminal solubility was similar to the maximum effect previously observed after concomitant soymilk intake (6-fold increase in AUC) [8].
- Simulated lumefantrine PK in virtual pediatric populations (0.5-5 yr, non-malnourished and severely malnourished), adopting the standard three-day oral twice-daily dosing of 120 mg, agreed well with clinical observations in respective population (Figure 3) [9].

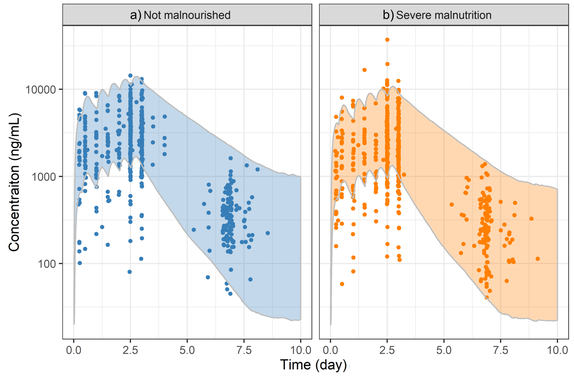

Figure 3. *Concentration-time profiles (log-linear scale) at oral 120 mg b.i.d. 3d in **a)** non-malnourished and **b)** severely malnourished pediatric populations. Clinical observations (individual measurements) are represented by dots while shaded areas represent the predicted 5–95% quantiles for virtual populations using the developed lumefantrine PBPK model.*

- Although receiving a higher dose per kg, the lumefantrine exposure, maximum concentration (C_{max}) and concentration at day 7 (C_{7d}) were lower in severely malnourished children compared to non-malnourished children.
- Dose investigation predictions showed that large dose adjustments are needed to reach similar plasma levels in severely malnourished children as in non-malnourished (Table 1). This indicates that the conventional dosing schedule (b.i.d. 3d) cannot be applied for adequate treatment of malnourished children (Table 1).

Table 1. *Predicted difference in AUC, C_{max} and C_{7d} due to severe malnutrition and estimated dose adjustment (folds) required to match each parameter in non-malnourished state. Simulations performed using BWT based dose regimen and single dose administration.*

PK measurement	AUC	C_{max}	C_{7d}
Malnourished compared to non-malnourished at same BWT based dose (ratio)	0.70	0.81	0.54
Required BWT based dose adjustment in malnourished to match parameter in non-malnourished (folds)	×10	×7.1	×4.8

Conclusions

- The PBPK approach was able to describe and predict lumefantrine PK in severely malnourished children.
- Results demonstrate that additional dosing occasions to the traditional three-days dosing regimen is needed to reach therapeutic targets in severely malnourished children.
- Adjustments to dosing for fixed dose combination drugs may need specific consideration due to drug specific consequences of malnutrition and dose non-linearities.

- Predictions suggest that addition of one day of dosing, with the same daily dose, to the conventional dose regimen, i.e., b.i.d. 4d., would be adequate to achieve similar lumefantrine exposure and C_{7d} levels in severely malnourished as in a non-malnourished children.

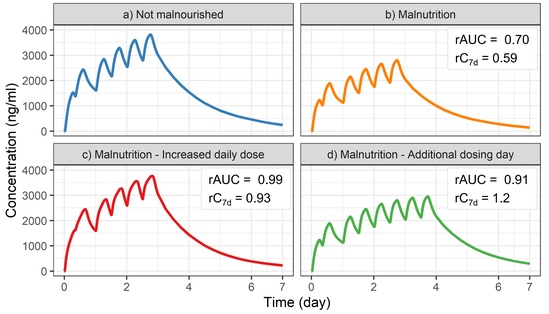

Figure 4. *Simulated lumefantrine concentration-time profiles in a typical child (1 year) at a non-malnourished state (**a**) or at severe malnutrition (**b**, **c** and **d**). Lumefantrine dosing either as 120 mg b.i.d. (**a**, **b** and **d**) or 890 mg (**c**) b.i.d. for 3 days (**a**, **b**, **c**) or 4 days (**d**). AUC and C_{max} ratio calculated using non-malnourished state measures as reference.*

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