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FAKULTÄT FÜR MATHEMATIK, INFORMATIK UND NATURWISSENSCHAFTEN

POPULATION PHARMACOKINETICS OF ATOVAQUONE - FROM INFANTS TO ADULTS

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Introduction

The development of resistance to the artemisinin combination therapy (ACT), which is the WHO recommended first line treatment in all malaria endemic countries [1], has been a rising concern. A declining efficacy of the ACT has been observed in the last decade in the Greater Mekong Region in South East Asia (SAE). Epidemiological genomic studies confirmed that artemisinin resistance had developed [2]. At the same time, resistance to the partner drugs developed, causing a decline in cure rates of the ACT in SAE [3]. New combination therapies are needed to halt the emergences of resistance and increase the curing rates. In a proof of concept Phase II trial new combination therapies were tested in children and adults with uncomplicated Malaria in Ghana and Gabon. In this analysis our aim was to describe the pharmacokinetics of atovaquone with this new combination.

Methods

40 patients between 6 month and 65 years were given the new combination therapy consisting of artesunate/pyronaridine and atovaquone/proguanil. The atovaquone doses were adjusted to the weight of the patients according to the official dosing recommendation [4]:

- 5-8 kg: 125 mg (0, 24h, 48h)
- 9-10 kg: 187.5 mg (0, 24h, 48h)
- 11-20 kg 250 mg (0, 24h, 48h)
- 21-30 kg: 500 mg (0, 24h, 48h)
- 31-40 kg: 750 mg (0, 24h, 48h)
- >40 kg: 1000 mg (0, 24h, 48h)

Samples were taken up to day 42 after treatment start with a dense sampling scheme after the first dose to identify the absorption phase of the drug. The sampling was reduced depending on the weight of the patient. The samples available for modelling can be seen in figure 1.

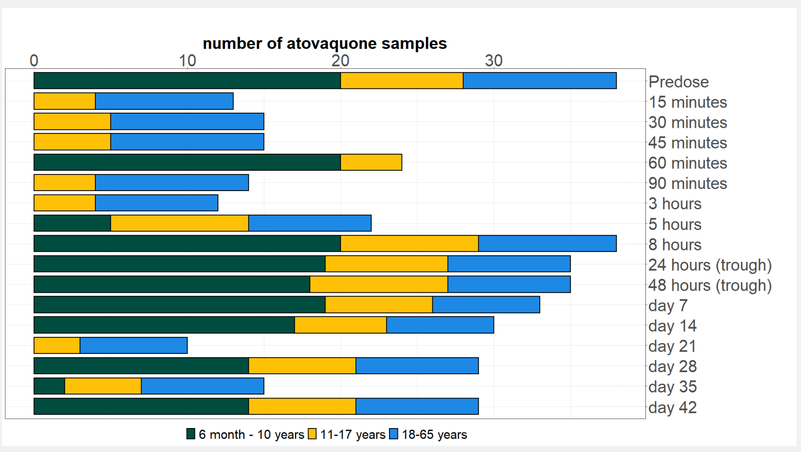

Figure 1 Samples available for modeling. Each sampling time point is stratified by age.

We developed and validated a LC-MS method to quantify atovaquone concentrations in plasma with a limit of quantification (LOQ) of 25 ng/mL. The distribution of samples above the LOQ can be seen in figure 2. Pharmacokinetic analysis was performed using non-linear-mixed- effect modeling in NONMEM® 7.5. 409 samples were available for analysis with 236 samples above the limit of quantification.

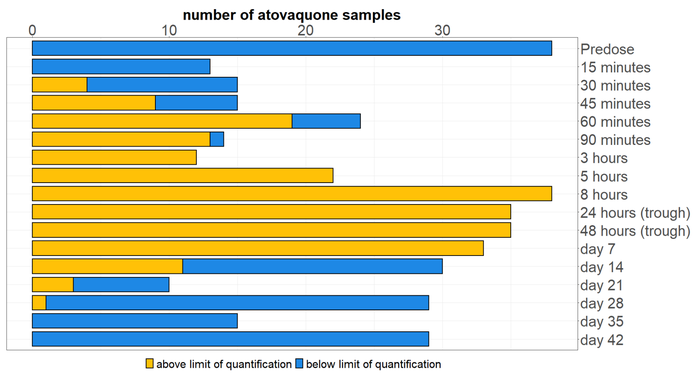

Figure 2 Samples available for modeling. Each sampling time point is stratified by the fraction of samples above the limit of quantification

Results

1-, 2 and 3- compartment models with linear and non-linear (Michaelis-Menten) elimination were tested. We found a 2-compartment model with linear-elimination to be the most suitable model. The absorption was modeled using a lag-time which was estimated to 0.5 h. To stabilize the final model the lag time was fixed. Inter individual variability (IIV) was supported on clearance (CL) and the central volume of distribution (V1) as well as the absorption constant (KA) and lag time. Weight was implemented as a covariate on clearance processes and the volumes as seen in figure 3. Using allometric scaling [ΔOBJ: -74.4] led to a smaller drop in objective function than estimating the exponents [ΔOBJ: -81.8]. Therefore the model estimating the exponents was chosen. A maturation function was tested on clearance but did not improve the model fit.

$$CL = TVCL * \left(\frac{Weight\ [kg]}{70\ kg}\right)^{COV_{Weight_{CL,Q}}}$$

$$V1 = TVV1 * \left(\frac{Weight\ [kg]}{70\ kg}\right)^{COV_{Weight\_V1,V2}}$$

$$Q = TVQ * \left(\frac{Weight\ [kg]}{70\ kg}\right)^{COV_{Weight_{CL,Q}}}$$

$$V2 = TVV2 * \left(\frac{Weight\ [kg]}{70\ kg}\right)^{COV_{Weight\_V1,V2}}$$

Figure 3 The effect of weight is implemented as a power model centered around 70 kg for both clearance parameters (clearance (CL) and intercompartmental clearance (Q)) and volumes (central (V1) and peripheral (V2) volume of distribution)

Table 1 Final model estimates of the 2-compartment model with their 95% confidence interval (CI)

Parameter	Value	95%CI
Clearance (CL/F) [L/h]	16.2	11.4 – 21.3
intercompartmental clearance (Q/F) [L/h]	2.19	0.24 – 4.37
central volume (V1/F) [L]	858.0	647.5 – 1436.3
peripheral volume (V2/F) [L]	111.2	75.4 – 214.4
absorption constant (KA)	0.25	0.17 – 0.34
Lag time [h]	0.5	Fixed
F fraction vomit	0.05	Fixed
$COV_{Weight\_CL,Q}$	1.0	0.70 – 1.3
$COV_{Weight\_V1,V2}$	1.3	0.96 – 1.8
IIV CL [%CV]	49.5	34.0-61.8
IIV V1 [%CV]	75.0	39.1 – 98.6
IIV KA [%CV]	123.9	80.3-192.0
IIV lag time [%CV]	50.7	36.7 -66.2
Proportional error [%CV]	33.3	27.8-40.6
Additive error [ng/mL]	1.7	1.1 – 2.4

The final model was run without the data below the quantification limit (BQL) censored and with the BQL data censored. Bootstraps using 3000 samples were performed with both models. As the parameter estimates did not significantly change the BQL data was used in the final model. Final model parameters with their 95% confidence interval are listed in table 1. Goodness of fit plots and visual predictive checks (VPC) were performed to evaluate the model fit. The VPC of the final model can be seen in figure 4. AUC_{24h} after the last dose was determined for all patients and is shown stratified in weight groups in figure 5.

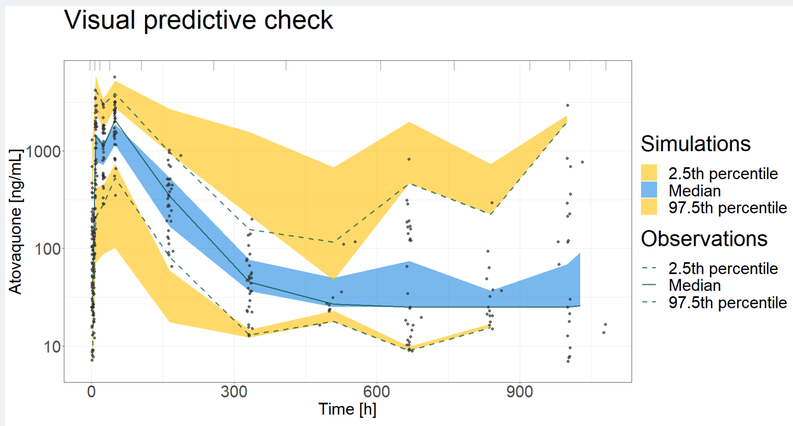

Figure 4 Prediction corrected visual predictive check of the final model; n=1000 simulations

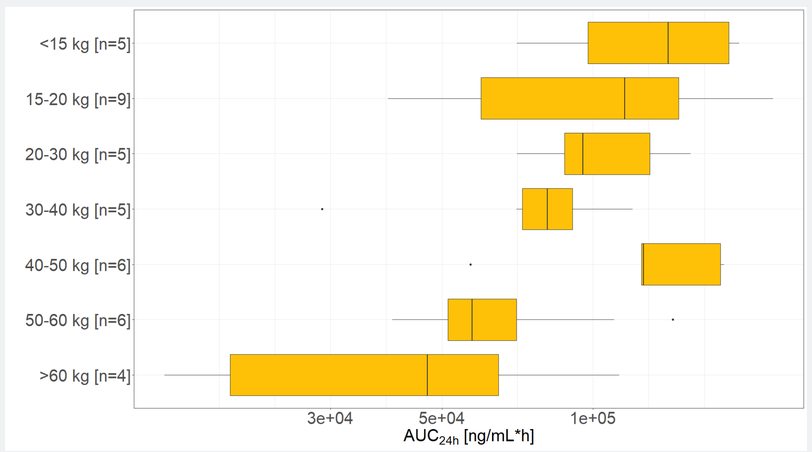

Figure 5 AUC_{24h} after the last dose for all patients. Stratified into different weight groups.

Conclusion

The model adequately described the PK of atovaquone. We found the absorption process to be the main driver for IIV, with a high IIV on KA and the lag time. The trough concentrations were slightly underpredicted. As atovaquone is almost entirely eliminated through bile and is mostly unmetabolized it is possible that enterohepatic recirculation (EHC) effects the clearance [4].When inspecting the raw data, in a few patients this behavior was observed.

We found the AUC_{24h} after the last dose to be significantly higher in patients below 50 kg (<50kg = $33.8*10^3$ ng/mL*h - >50kg = $19.9*10^3$ ng/mL*h, p=0.028). The dose is not further increased for patients >40 kg. This might explain the reduction in AUC in this weight group.

In a next step we will try to implement the EHC in the model. Finally, we will add pharmacodynamic data (parasite density) to the model to explore the exposure response relationship of atovaquone.

Literature

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[5] Rolan PE, Mercer AJ, Tate E, et al. Disposition of atovaquone in humans. Antimicrob Agents Chemother. 1997;41:1319–21.

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