A Bayesian Population Pharmacokinetic Analysis of Oritavancin in Pediatric Skin Infection Patients

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INTRODUCTION

Oritavancin is a glycopeptide antibiotic approved in adults for the treatment of acute bacterial skin and skin structure infections (ABSSSI) with a single IV dose of 1200 mg. Sparse pharmacokinetic (PK) data are available from two ongoing pediatric studies with age groups of 0 to <3 months, 3 months to <2 years, 2 to < 6 years, 6 to < 12 years, and 12 to < 18 years. Tested pediatric dosages included 15 and 20 mg/kg IV.

OBJECTIVES

Characterize the pediatric PK of oritavancin with a population PK (popPK) model and perform stochastic simulations to support pediatric dose selection.

METHODS

Dataset: Sparse PK data from pediatric patients (N=104, including 3 neonatal patients aged < 3 months) were combined with sparse PK data from two pivotal Ph3 studies of adult patients with ABSSSI (N=297).

Model: A three-compartment model with linear elimination was fit to the combined dataset using the Markov Chain Monte Carlo (MCMC) algorithm in Pumas software.

Priors: Parameter estimates from a previous popPK model [1] were used as Bayesian priors. This model was developed with data from Ph1, Ph2 and earlier Ph3 studies (N=560 subjects) with mostly dense PK sampling. Priors of 0.75 and 1 were used for clearance and volume allometric exponents, respectively.

Covariates: After fitting the base model, weight was assessed as a covariate on clearance and volume parameters with allometric scaling.

Simulations: Stochastic simulations were performed using a virtual population (N=1000 per sex and year of age) created by sampling from CDC growth chart weight distributions.

Probability of target attainment: PTA was assessed against *Staphylococcus aureus* using a previously established AUC(0-72)/minimum inhibitory concentration (MIC) ratio target.

RESULTS: MODEL DEVELOPMENT

Table 1: The base and final model with allometric scaling using Bayesian priors was successfully fit to the combined adult and pediatric dataset. All MCMC diagnostics showed adequate convergence of the chains. Parameter estimates of the final model are shown below.

Parameter [Units]	Mean Estimate	95% Credible Interval
Fixed Effects		
Clearance [L/h]	0.431	0.418 – 0.445
Volume of central compartment [L]	5.96	5.78 – 6.15
Intercompartmental clearance 1 [L/h]	0.824	0.784 – 0.865
Volume of peripheral compartment 1 [L]	13.4	13.0 – 13.7
Intercompartmental clearance 2 [L/h]	0.296	0.280 – 0.314
Volume of peripheral compartment 2 [L]	104	99.7 – 109
WT on CL	0.779	0.711 – 0.848
WT on V1	0.788	0.716 – 0.865
WT on Q2	0.604	0.504 – 0.713
WT on V2	1.15	1.05 – 1.26
WT on Q3	0.890	0.776 – 1.01
WT on V3	0.862	0.717 – 1.03
Random Effects		
ηCL %CV	0.170	0.148 – 0.192
ηV1 %CV	0.108	0.0919 – 0.126
ηQ2 %CV	0.353	0.288 – 0.427
ηV2 %CV	0.131	0.106 – 0.160
ηQ3 %CV	0.471	0.405 – 0.545
ηV3 %CV	0.250	0.205 – 0.289
Residual Error		
Proportional Error [%]	0.272	0.256 – 0.289
Additive Error [µg/mL]	0.193	0.097 – 0.266

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RESULTS: MODEL EVALUATION

Figure 1: Although the base model showed trends of etas with body weight for most parameters, the final model with allometric scaling did not show any correlations of etas with body weight or age (not shown).

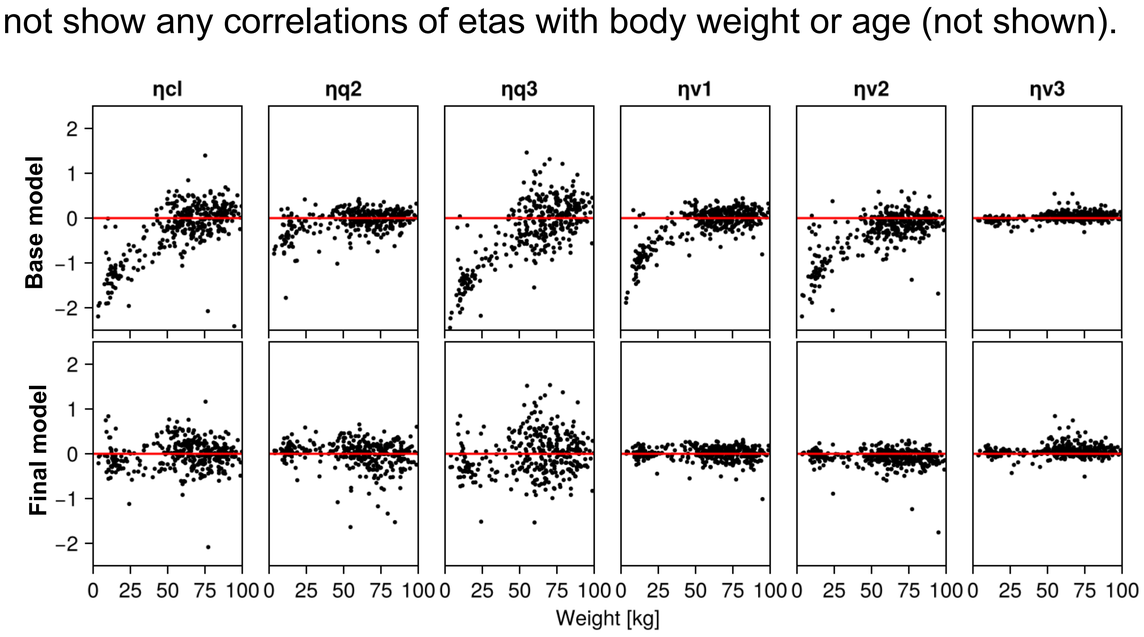
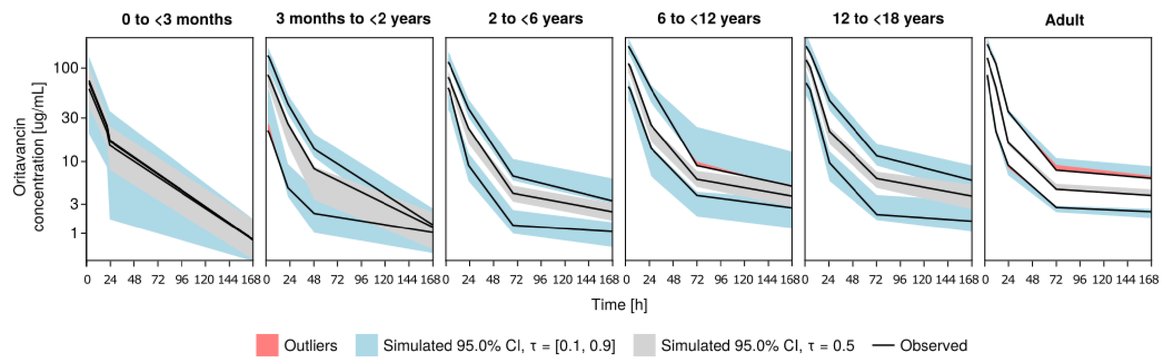


Figure 2: The final model adequately described the PK of each age group as demonstrated by an age-stratified visual predictive check (VPC).



RESULTS: SIMULATIONS

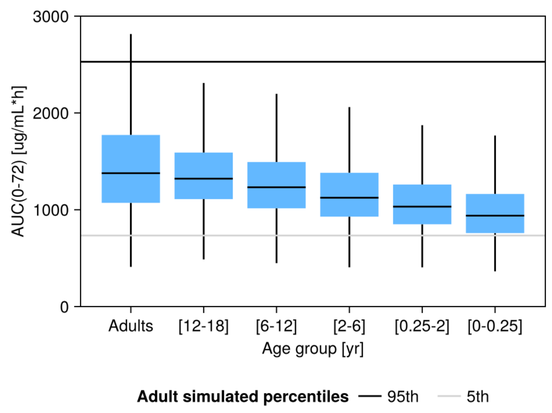


Figure 3: Stochastic simulations of 15 mg/kg (the MTD in pediatrics) predicted that neonates have a median AUC(0-72) below the 25th percentile of adults. The median of other exposure metrics (Cmax and AUC(72-168) approached the adult 5th percentile.

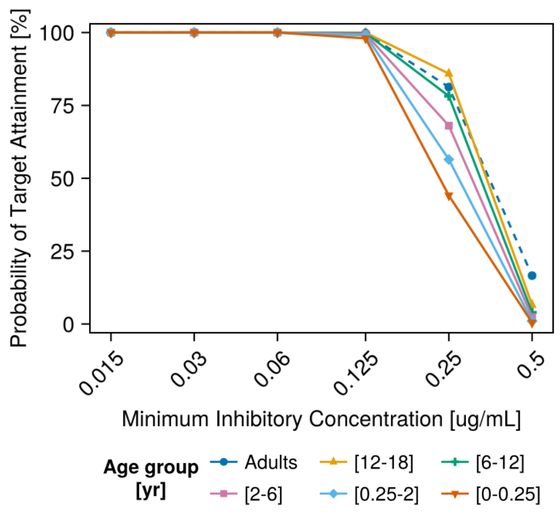


Figure 4: PTA analysis of exposures in neonates following a 15 mg/kg dose showed a reduced probability of efficacy against *Staphylococcus aureus* net bacterial stasis at an MIC of 0.25 µg/mL compared to an adult receiving the approved 1200 mg dose.

CONCLUSIONS

- The PK of oritavancin in pediatric and adult patients with ABSSSI was adequately described by a Bayesian three-compartment model.
- No trend of age with clearance was identified after controlling for the effect of body weight.
- Simulated exposures in neonates < 3 months of age were potentially sub-therapeutic at the maximum tolerated dose of 15 mg/kg.

[1] Rubin CM, Van Wart SA, Bhavnani SJ, Ambrose PG, McCollam JS, Forrest A. Oritavancin population pharmacokinetics in healthy subjects and patients with complicated skin and skin structure infections or bacteremia. 2009. Antimicro Agents Chemother, 53:4422-8.