Title: Clinical trial simulations to assess the influence of population pharmacokinetic model selection on initial dosing recommendations of vancomycin in neonates

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Background: Vancomycin remains the primary treatment for severe methicillin-resistant Staphylococcus aureus (MRSA) infections, with optimal dosing and monitoring presenting ongoing challenges to clinicians despite its long-standing clinical use and nearly 100 published population pharmacokinetic models. This study aims to evaluate the concordance of optimal initial simulated doses among various vancomycin models developed for neonates and to explore the role of model predictive performance in explaining the variability in probability of target attainment (PTA).

Methods: A virtual neonatal patient population (n=1500) receiving vancomycin therapy was simulated through 130 clinical trial simulations, testing five dosing regimens using 26 population PK models previously evaluated in a neonatal population at Sainte-Justine Hospital, Montreal. Simulated regimens included loading doses ranging from 15 to 20 mg/kg and maintenance doses ranging from 10 to 15 mg/kg administered every 6 to 12 hours. For each simulated study, the area under the concentration-time curve (AUC24) and PTA was calculated to determine the optimal regimen per model and to assess the agreement on initial doses across the 26 models. A multiple regression was performed to explore the impact of the models' predictive performance on PTA. All PK analyses were performed on NONMEM v7.5. Statistical analyses and data visualization were performed on R.

Results: For most models (15/26), there was an agreement on the optimal dosing regimen: a 15 mg/kg loading dose followed by an 11 mg/kg maintenance dose every 8 hours. AUC24 values across all models did not achieve a PTA (AUC24 400-600 mg·h/L) > 50%, with the highest PTA being achieved by the model with the best a priori predictive performance. The multiple regression model significantly predicted mean ln-transformed PTA, with $F(2, 23) = 5.406$ and $p = 0.01$, yielding an adjusted R^2 of 0.26. PTA was significantly influenced by imprecision ($p=0.048$) but not bias ($p=0.469$).

Conclusions: In conclusion, our study demonstrated that, despite the variability in bias and imprecision among models, there was a consensus on the initial optimal doses for the majority of models; however, models with superior predictive performance yielded higher PTA values. We established that bias and imprecision alone do not sufficiently predict PTA, with imprecision having a more pronounced effect.

Key words: vancomycin, population pharmacokinetics, external evaluation, therapeutic drug monitoring