Development of a PBPK Model for Vancomycin in a Population with Impaired Renal Function Using Simcyp Simulator
T. Vora1, K. Martinez2, L. Camaione2, T. Le2, D. Taft1
1Long Island University, 2Brooklyn Hospital Center

Purpose
To develop and validate a Simcyp model for vancomycin in a healthy population and to evaluate the predictability of the model to simulate the vancomycin pharmacokinetics in patients with impaired renal function.

Methods
PBPK modeling with the Simcyp Simulator was used to simulate serum vancomycin concentrations after IV-infusion (1 g over 40 minutes) in healthy volunteers. Pharmacokinetic parameters (e.g., Vss and Cl) were determined. The model was validated against published data reporting vancomycin pharmacokinetics after dosing to healthy subjects and morbidly obese patients. The model was then used to simulate the serum concentration vs. time profiles for adult patients with varying degrees of renal insufficiency, using three subsets based on GFR: (1) GFR less than 30 mL/min, (2) GFR between 30-60 mL/min, (3) GFR more than 60 mL/min. The model predictions were then compared to steady state serum trough concentration measured in patients (n = 69) treated with vancomycin for methicillin-resistant Staphylococcus aureus (MRSA). These data were obtained from medical records of The Brooklyn Hospital Center along with demographic information, serum creatinine levels (on admission and during treatment) and dosing information. Glomerular filtration rate (GFR) was calculated for each subject using Cockcroft-Gault equation. Based on the medical record data, Simcyp simulations were performed across the three population subsets over a range of doses, dosing frequencies and infusion durations. The fold prediction error between predicted and observed values were calculated.

Results
Model estimates of vancomycin Cl (5.27 ± 0.37 L/hr) and Vss (0.34 ± 0.09 L/kg) compared favorably with published data from healthy subjects. A plot of predicted and observed serum concentration-time profiles is provided in Figure 1. The model was able to capture observed steady state trough concentrations for vancomycin within model-predicted 95% confidence intervals in all three sub-populations of patients with renal insufficiency. Prediction fold error for simulated and observed data is tabulated in Table 1. The prediction error was within 2-fold for 76.8% of the patients studied. The prediction error was within 3-fold in 85.5% of all subjects tested. For several subjects with prediction errors above 3-fold, there were discrepancies in reported serum creatinine values between the time of admission and during treatment. When patients were stratified based on GFR during therapy, 84.1% and 91.3% of patients observations were predicted within 2- and 3-fold error, respectively.

Conclusion
A PBPK model for vancomycin was developed and validated using the Simcyp Simulator. The model was successfully applied to predict drug exposure in patients with varying levels of renal insufficiency. The model is a potentially useful tool for selecting vancomycin doses in renally compromised patients to achieve targeted serum profiles, although further study is needed to utilize this model in clinical research.

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References

Figure 1: Steady state serum vancomycin concentration after 9th dose of 10 g of vancomycin IV-infusion over 1 hr ± 12 hr in control subjects.