Title: Population Pharmacokinetics of Intermittent Vancomycin in Cystic Fibrosis Patients

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Introduction: Methicillin-resistant *staphylococcus aureus* (MRSA) infections are one of the leading causes of pulmonary exacerbations (PEx) in persons with cystic fibrosis (PwCF). It is found in 25% of PwCF, and its prevalence is increasing in this population [1]. Treatment of PEx in this population often requires hospitalization, including increased respiratory treatments and intravenous (IV) antimicrobials. IV vancomycin is used as a first-line agent to treat MRSA infections in PwCF [2]. The dosing guidelines for vancomycin in PwCF vary widely among various institutions, and the most common dosing reported has a wide range of 15 to 20 mg/kg/dose every 8 to 12 hours [3]. Despite its broad use in PwCF, there is limited information on the pharmacokinetics of intermittent dosed IV vancomycin in this population [4]. Furthermore, there are no reports in the literature that have characterized the population pharmacokinetics of IV intermittent-dosed vancomycin in adult PwCF. A well-characterized population pharmacokinetic model can identify and quantify sources of variability in vancomycin concentration in PwCF and guide individualized dosing of vancomycin in this population, which could potentially improve clinical outcomes.

Objectives: The primary objective of this research is to evaluate the pharmacokinetics of vancomycin after intermittent intravenous dosing in adults PwCF using a population pharmacokinetic approach and to identify covariates that significantly influence vancomycin pharmacokinetics in PwCF. The secondary objective of this research is to apply the population pharmacokinetic model using Monte Carlo simulation to obtain the probability of achieving desired vancomycin target exposures (AUC > 400 mg*hr/L) under different dosing regimens.

Methods: PwCF older than 18 years who were admitted to the University of Utah Hospital between May, 2014 and August 2020 were identified for this study (n=14). The peak and trough plasma concentrations of vancomycin in these patients after intermittent intravenous dosing were obtained from the electronic health records. Vancomycin pharmacokinetic parameters were evaluated using NONMEM® 7.5, Perl-speaks-NONMEM (PsN®) version 5.3.0, Finch Studio™, and R package. The data was fitted with one- and two-compartment first-order conditional estimation with interaction models. Potential covariates tested include weight, age, sex, creatinine clearance, and use of concomitant medications. Creatinine clearance was calculated using the Cockcroft-Gault equation [5], and the list of concomitant medications included inhaled tobramycin and inhaled aztreonam. Models were compared by assessing the objective function value (OFV), and a reduction in OFV of more than 3.84 was considered statistically significant ($p < 0.05$). The Monte Carlo simulations (n=1000) based on the commonly reported intermittent vancomycin dosing in PwCF (500-2000 mg every 12 hours) were performed to determine the optimal dosing regimen.

Results: A total of 181 trough and peak concentrations in 14 PwCF were included in the analysis. The median (range) vancomycin dose patients received was 750 mg (500-2000 mg), and the dosing frequency ranged from every 8 hours to every 12 hours. The median (range) for; age was 24 years (19–58 years), weight was 52.6 kg (41–106 kg), creatinine clearance was 106 mL/min (36.4–183 mL/min range), and vancomycin concentration was 19.8 mg/L (6.6– 61.4 mg/L). A one-compartment model with a first-order elimination rate with a proportional error model best described the data. Weight significantly influenced vancomycin clearance ($p<0.001$) and vancomycin clearance increased with an increase in weight. In the final model, vancomycin clearance was estimated as 5.52 L/h/70 kg, and the volume of distribution was 31.5 L/70 kg. The between subject variability for clearance was 23.3%. The residual unexplained variability was 20.3%. The simulations data showed that 72% of virtual patients in the 2000 mg every 12-hour dosing group reached the target AUC > 400 mg*h/L. However, further pharmacodynamic studies are needed to confirm the simulation results.

Conclusion: The pharmacokinetics of vancomycin in adult PwCF after intermitted intravenous administration were adequately described using a population pharmacokinetics modeling approach. We also demonstrated that the model could be used to perform simulations of various vancomycin intermittent dosing regimens to optimize dosing of vancomycin in adult PwCF.

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