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Model-informed simulation for optimal vancomycin dosage in pediatric patients with febrile neutropenia: implication of augmented renal clearance on appropriate dosing: Shimamoto Y[1], Mizuno T[2,3], Verstegen R[1], Allen U[4], Ito S[1,5]

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Background

Febrile neutropenia (FN) is a severe complication in patients following Hematopoietic Stem Cell Transplant (HSCT). Vancomycin (VCM) is used to treat patients with FN. In pediatrics, the recommended VCM dosage is 60 mg/kg/day irrespective of age and renal function. However, an increased renal function known as augmented renal clearance (ARC) is often seen in patients with FN, which causes insufficient VCM exposure. In this study, we identified age-appropriate VCM dose regimens in children with FN by using population pharmacokinetics (PK) modeling and simulation.

Methods

Children (0-17 year) with FN treated with VCM following HSCT between 2009-2014 were enrolled. Population PK analysis was performed using NONMEM. The effect of body size and organ maturation were described by allometrically scaled weight and a sigmoidal Emax model based on postmenstrual age (PMA), respectively. Monte Carlo simulation was performed using the developed PK model to identify dosing regimens improving the target attainment based on age and renal function in this population.

Results

A total of 276 VCM plasma concentrations obtained from 165 patients were available. Body weight, PMA, estimated glomerular filtration rate (eGFR) and body temperature were identified as a significant covariate on VCM clearance. The estimated VCM clearance was 5.99 L/h/70kg, which was higher than that in previous reports in children without FN. The median eGFR (143 mL/min/1.73m^2) was higher than the population average, and 36% and 34% of patients showed an eGFR of 120-160 and >160 mL/min/1.73m^2, respectively. A total of 48 different dosing regimens (8 eGFR cohorts across 6 different age cohorts) were identified to achieve the target AUC/MIC of 400-650, a recommended range for Methicillin Resistant Staphyllococcus Aureus infection. In our analysis, 1-2 year old children with an eGFR of 160 mL/min/1.73m^2 require a 50% higher dose (i.e., 90 mg/kg/day) compared to the current recommendation.

Conclusions

We successfully identified an increased VCM clearance attributed to an increased eGFR by ARC in children with FN. Dosing simulations indicated that children with FN require higher doses than the current standard dose to improve target exposure attainment.

Key Words: Pharmacokinetics, Vancomycin, Pediatrics, Febrile neutropenia, Augmented renal clearance