Bayesian Estimation of Vancomycin Pharmacokinetics in Obese Children: Matched Case-Control Study

Jennifer Le, PharmD, MAS, FCCP, FCSHP, BCPS-ID[1,2]; Edmund V. Capparelli, PharmD[1]; Uzra Wahid, PharmD[1]; Yi Shuan S. Wu, BS[1]; Gale L. Romanowski, PharmD[3]; Tri M. Tran, BS[2]; Austin Nguyen[2]; and John S. Bradley, MD[1,3]

[1]University of California, San Diego, Skaggs School of Pharmacy and Pharmaceutical Sciences and School of Medicine, La Jolla, California; [2]Miller Children's Hospital of Long Beach, Long Beach, California; and [3]Rady Children's Hospital of San Diego, San Diego, California

ABSTRACT

Purpose: The study objective was to compare different body size descriptors that best estimate vancomycin V_d and clearance (CL).

Methods: Patients between 3 months and 21 years old who received vancomycin for ≥48 hours from 2003 to 2011 were evaluated in this matched case-control study. Cases had body mass index in the ≥85th percentile; controls were nonobese individuals who were matched by age and baseline serum creatinine (SCr). Using a 1-compartment model with first-order kinetics, Bayesian post hoc individual V_d and CL were estimated.

Findings: Analysis included 87 matched pairs with 389 vancomycin serum concentrations. Median ages were 10.0 (interquartile range [IQR], 4.8–15.2) years for cases (overweight and obese children) and 10.2 (IQR, 4.5–14.8) years for controls (normal-weight children). Median weights were 44.0 (IQR, 23.4–78.1) kg for cases and 31.3 (IQR, 16.8-47.1) kg for controls. Mean (SD) for the baseline SCr values were also similar between the groups: 0.51 (0.22) (IQR, 0.34–0.67) mg/dL and 0.48 (0.20) (IQR, 0.30–0.60) mg/dL for the cases and controls, respectively. Actual weight and allometric weight (ie, weight$^{0.75}$) were used in the final model to estimate V_d and CL, respectively. The mean V_d and CL, based on weight, for cases were lower than controls by 0.012 L/kg and 0.014 L/kg/h, respectively.

Implications: In obese children, actual weight and allometric weight are reasonable, convenient estimations of body fat to use for estimating vancomycin V_d and CL, respectively. However, these pharmacokinetic differences between obese children and those with normal weights are small and may not likely to be clinically relevant in dose variation. (*Clin Ther*. 2015;37:1340–1351)

Key words: antibiotics, children, obesity, pediatrics, pharmacokinetics, *Staphylococcus aureus*, vancomycin.

INTRODUCTION

Vancomycin is a first-line antibiotic for treating invasive methicillin-resistant *Staphylococcus aureus* infections.[1] The pharmacokinetic (PK) profile and dosing information of vancomycin for obese children remain suboptimal. Coupled to the age-related PK variation between adults and children, excessive adipose tissue (ie, obesity) may significantly affect the distribution and clearance of drugs. With the extensive use of vancomycin in pediatrics and an epidemic of obesity, we believe that it is essential to first analyze the PK parameters of vancomycin that are necessary to optimize dosing in obese children, especially in light of limited population-based PK studies.[1]

Previous PK studies on vancomycin dosing in obese pediatric and adult patients evaluated different body size descriptors (primarily total weight and secondarily lean body mass [LBM] and ideal weight [IW]) for estimating V_d and clearance (CL).[2–7] In obese adults, weight-adjusted V_d was decreased, whereas weight-adjusted CL was either similar or decreased.[4–7] Pediatric studies did not yield

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significant conclusions regarding differences in weight-adjusted V_d and CL.[2,3,8,9] Notably, none of these pediatric PK studies used Bayesian analysis, which is better in predicting V_d and CL in an obese population based on an understanding of the population PK properties and interindividual and intraindividual variability.

With the limited population-based PK studies that incorporate Bayesian estimation, we aimed to compare 7 different measures of body size descriptors, including actual weight, adjusted weight (AW), IW, allometric weight (ALWT), body mass index (BMI), body surface area (BSA), and LBM, and their influences on vancomycin V_d and CL and in overweight and obese children. Enhancing the accuracy in estimating V_d and CL would result in better empiric dosing recommendation in this population to rapidly achieve a therapeutic exposure without unnecessary vancomycin renal toxicity.

PATIENTS AND METHODS

This matched case-control study was conducted at 2 children's hospitals. Miller Children's Hospital of Long Beach is a community-based, tertiary care, teaching hospital with 249 beds (34 pediatric intensive care, 69 neonatal intensive care, 94 general pediatrics, and 52 hematology/oncology beds). Rady Children's Hospital of San Diego is a tertiary care, teaching hospital with 308 beds (44 pediatric intensive care, 49 neonatal intensive care, 177 general medical/surgical, and 38 hematology/oncology beds). This study was approved by the institutional review boards at these institutions with the use of a waiver of informed consent for retrospective, deidentified data collection and analysis.

As part of routine patient care at Miller Children's Hospital of Long Beach and Rady Children's Hospital of San Diego, clinical pharmacists conduct therapeutic drug monitoring for all patients receiving vancomycin. Patients were monitored daily while they were taking vancomycin; blood samples to evaluate vancomycin concentrations were generally obtained after the third dose. The entire dosing history and measured serum concentrations, in the context of the timing of the blood sample after vancomycin infusion, were used in the PK modeling. Renal function was monitored closely using serum creatinine (SCr).

Data Collection

Patients aged 3 months to 21 years were included if they received vancomycin for $\geq$48 hours from September 1, 2003, through July 30, 2011, and had $\geq$1 serum vancomycin concentration collected within $\leq$96 hours of drug therapy initiation. Patients were excluded if they were undergoing hemodialysis or receiving amphotericin B formulations or immunosuppressive medications, including cyclosporine, tacrolimus, and sirolimus, which may have interfered with vancomycin CL within 7 days before or during vancomycin therapy. Demographic characteristics (eg, sex, age, weight, and height) and clinical and laboratory data (eg, SCr and vancomycin concentrations) were extracted for each patient on standardized case report forms. The growth charts from the Centers for Disease Control and Prevention were used to categorize overweight and obesity based on age and sex.[10] Overweight was defined as weight or BMI in the 85th to 94.9th percentile and obesity at the $\geq$95th percentile.[11] Actual body weight was used to categorize overweight or obesity in patients $<$2 years old and BMI for those $\geq$2 years old. Overweight and obese patients served as cases and were matched to controls consisting of individuals with normal weights. Matching criteria were age (within 1 year), SCr (within 0.4 mg/dL), the use of concurrent nephrotoxic medications, and stay in the intensive care unit. Different measures of body composition were calculated using various equations (Table I).

Population-Based PK Model

Assays to measure serum vancomycin concentrations and SCr at each study site have been published previously.[21] Population-based PK analyses were performed using the nonlinear mixed-effect modeling software NONMEM, version 7.2 (Icon, Dublin, Ireland), and Perl-Speaks-NONMEM, version 3.7.6 (Free Software Foundation using General Public License). Because most vancomycin samples were collected after the distribution phase, a 1-compartment model was used to describe the vancomycin PK parameters V_d and CL. On the basis of a large population-based PK study in children, age and SCr were identified as important covariates for CL.[21] Consequently, these measures were included as covariates in the base model, and different measures of body size descriptors were evaluated in subsequent intermediate models.