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Hospitalized Patients with and without Hemodialysis Have Markedly Different Vancomycin Pharmacokinetics: A Population Pharmacokinetic Model-Based Analysis

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Abstract

Background

Despite being in clinical use for about six decades, vancomycin dosing remains perplexing and complex.

Methods

A population pharmacokinetic modeling and simulation approach was used to evaluate the efficiency of the current nomogram-based dosing of vancomycin. Serum vancomycin concentrations were obtained as a part of routine therapeutic drug monitoring (TDM) from two 500-bed academic medical centers. A population pharmacokinetic model was first built using these TDM data. Population pharmacokinetic modeling was conducted using NONMEM® (7.2 and 7.3). The forward addition–backward elimination approach was used to test the covariate

effects. Appropriate numerical and visual criteria were used as model diagnostics for checking model appropriateness and model qualification. The current nomogram efficiency was evaluated by determining the percentage of subjects in the therapeutic range (10 to 20 mg/L).

Results

A two-compartment model with between-subject variability on clearance (CL), central volume of distribution (Vc), and peripheral volume of distribution (Vp) best fit the data. Blood urea nitrogen, age, creatinine clearance, and hemodialysis status were significant covariates on clearance. Hemodialysis status was a significant covariate on Vc and Vp. In the final model, creatinine clearance was retained as a covariate on CL whereas hemodialysis status was retained as covariate on both CL and Vc. Using Monte-Carlo simulations, the current nomogram was optimized by the addition of a loading dose and reducing the maintenance doses. The current nomogram is suboptimal. Optimization of the nomogram resulted in >40% subjects consistently being in the therapeutic range at troughs collected after the first 6 doses.

Conclusions

CL and Vc differ markedly between patients undergoing hemodialysis and those not undergoing hemodialysis. Dosing nomogram based on these covariate relationships may potentially help in accurate dosing of vancomycin.

Keywords: Vancomycin, critically ill, hemodialysis, dosing

INTRODUCTION

Despite being in clinical use for about six decades, vancomycin dosing remains perplexing and complex. For most patients, nomograms are used, and more aggressive dosing has been employed to address the concern of the emergence of bacterial resistance.[1] A consensus review, endorsed by professional societies such as the Infectious Diseases Society of America, American Society of Health-System Pharmacists, and Society of Infectious Diseases Pharmacists evaluated the data for therapeutic monitoring of serum vancomycin concentrations and recommended maintaining trough serum vancomycin concentrations above 10 mg/L to avoid the development of resistant strains of bacteria.[2]

The pharmacokinetics of vancomycin has been described by one-,[3] two-,[4-6] and three-[7-9] compartment pharmacokinetics; several population pharmacokinetic models have been published, as well as a recent review on various models.[10] Vancomycin has a volume of distribution (V_d) ranging from 0.4 to 1 L/kg with variable distribution into the various tissues and body fluids.[2] A standard nomogram, using available pharmacokinetic data, has been used to help achieve targeted vancomycin concentrations.[11] However, in certain populations such as intensive care unit (ICU) and hemodialysis patients, the nomogram may not be directly or easily applicable. In critically ill patients, renal function is among the major factors that explains the observed differences in pharmacokinetics. The pharmacokinetics of vancomycin has been previously explored in critically ill patients.[12-15] Since vancomycin is predominantly eliminated by glomerular filtration, a decrease in renal function also decreases vancomycin total body clearance (CL). The elimination half-life ($t_{1/2}$) has been reported to range between 5.2 hours in patients with normal renal function to 7.5 days in patients with anuria.[4,9,16] Significant removal of vancomycin through high-flux membranes in hemodialysis and the rebound of vancomycin

concentration post hemodialysis are some other peculiarities in its pharmacokinetics.[17] Prior studies have focused on ICU and hemodialysis patients exclusively, or have had modest sample sizes, making it difficult to apply a single approach to pharmacokinetics of vancomycin in hospitalized patients including those with renal impairment or critical illness.

The objectives of this study were to develop a population pharmacokinetic model for vancomycin using retrospective data obtained from routine therapeutic drug monitoring (TDM), including patients undergoing intermittent hemodialysis, and evaluate the efficiency of current nomogram using Monte-Carlo simulations.

MATERIALS AND METHODS

The study protocol was approved by both Emory University and Mercer University institutional review boards (IRBs). A waiver was granted for informed consent.

Patient Population

A retrospective data analysis of routinely collected data was performed among patients aged >16 years hospitalized between January 1, 2011 and December 31, 2012 at two 500-bed academic medical centers serving a population with a high prevalence of end-stage renal disease who received at least one dose of intravenous vancomycin. Data extracted from the electronic medical records included the doses and date/time of each administration of vancomycin, date/time and value of vancomycin plasma concentration, demographics (age, sex, weight, height, and location (ward vs. ICU)); laboratory values (serum creatinine (SCr), blood urea nitrogen (BUN), osmolality); and hemodialysis status during that admission. The records of covariate values for subjects included in the analysis were complete without any missing information; therefore, no

covariate imputation was done. All hemodialysis procedures were intermittent and used high-flux membranes.

Bioanalytical Method

The vancomycin concentrations in serum samples collected as a part of TDM were determined by a validated ELISA method. The assay was the same for samples collected from both hospitals.

Population Pharmacokinetic Analysis

Software

Data management was conducted using R (version 3.1.2)[18] and Microsoft Excel (Microsoft Office 2010). Population pharmacokinetic modeling and simulations were conducted with NONMEM (ICON, Ellicott City, Maryland, version 7.2 and 7.3) by utilizing a gfortran (64-bit) compiler with Perl-Speaks NONMEM (PsN, version 3.5.3)[19] as an interface to run NONMEM. The first-order conditional estimation with interaction (FOCEI) algorithm was used for parameter estimation. Customized scripts in R (version 3.1.2) and XPOSE4[20] were used for goodness-of-fit (GOF) diagnostic plots.

Model development

One-, two-, and three-compartment models were evaluated as structural models. The ADVAN3 subroutine with TRANS4 parameterization was predominantly used in model development. Data that were below the limit of quantitation (BQL) were evaluated by the M3 method[21] or by exclusion of BQL data during model development. Modeling of between-subject variability (BSV) was done using an exponential relationship as follows:

$$\boldsymbol{\Theta_i} = \boldsymbol{\Theta_{pop}} \times \boldsymbol{e^{\eta_i}}$$

Θ_i is the individual pharmacokinetic parameter, Θ_{pop} is the population parameter, and η_i is the difference on natural log domain between Θ_i and Θ_{pop} with a mean 0 and variance ω^2. Residual variability was modeled as a combined additive and proportional model as follows:

$$\boldsymbol{Y_{ij}} = \boldsymbol{\widehat{Y_{ij}}}\boldsymbol{(1 + \varepsilon_{1ij})} + \boldsymbol{\varepsilon_{2ij}},$$

where Y_{ij} and $\widehat{Y_{ij}}$ represent the observed and predicted concentration in *i*th subject at *j*th time point, respectively. The residual error parameters $\boldsymbol{\varepsilon_{1ij}}$ and $\boldsymbol{\varepsilon_{2ij}}$ represent proportional and additive residual error components, respectively. They are assumed to have a normal distribution with mean 0 and variance of σ^2.

Model selection was based on several criteria such as the likelihood ratio test for hierarchical models, basic GOF plots, clinical and biological plausibility of parameter estimates, precision of parameter estimates, and condition number calculated by taking the ratio of largest to smallest eigenvalue obtained from the correlation matrix, which indicates the well-condition of the model. Successful convergence and covariance steps were considered in model selection in addition to the aforementioned elements. The GOF plots used were individual predictions (IPRED) and population predictions (PRED) vs observed concentrations, conditional weighted residuals (CWRES)[22] vs time, and CWRES vs PRED. The condition number was computed by taking the ratio of the highest to lowest eigenvalues obtained from the covariance step.

Based on careful consideration of prior clinical experience with vancomycin and potential future use of the model in clinical practice, covariates were selected for model development; they were as follows: BUN, osmolality, creatinine clearance (CrCL), body weight (WT), and hemodialysis status (DIAL). The "DIAL" variable was binary with a value of either 0 in the case of non-

dialysis subjects or a value of 1 in the case of dialysis subjects. CrCL was calculated by the Cockroft-Gault formula,[23] and CrCL greater than 150 ml/min was truncated to 150 ml/min.[24] Serum creatinine (Scr) values were truncated to 1 mg/dl if the Scr value was <1 mg/dl and the patient's age was >60 y and then these truncated SCr values were used in the CrCL calculation. The correction in Scr values in the elderly mirrors clinical practice and is applied to correct for falsely depressed Scr values in the elderly due to either lower muscle mass or decreased protein intake. A variable named "SAMP (=0 or 1)" was created such that SAMP=0 indicates patient with only one concentration of vancomycin and SAMP=1 indicates more than one concentration of vancomycin available for analysis. A joint variable combining DIAL and SAMP called "DISAM" was created with four categories: patients that were not on dialysis with only one concentration, patients that were on dialysis with only one concentration, patients that were not on dialysis with more than one concentration, and patients that were on dialysis with more than one concentration. Such categories based on DISAM were created for the purpose of checking for model misspecification during visual predictive checks and preserving the proportion of subjects in each DISAM category during bootstrap resampling. The resampling procedure in the bootstrap is with replacement; therefore, there is a risk that too few dialysis subjects or too few subjects contributing just one concentration will be included. Due to the impact of both dialysis status and number of concentrations in the estimation of population pharmacokinetic parameters, we thought it was necessary to preserve the proportion of subjects in the respective categories by creating the DISAM variable. The forward addition–backward elimination strategy also known as stepwise covariate model (SCM) building approach was adopted to test covariate effects.[25] In the forward addition steps of SCM, a covariate is added to base model and the drop in objective function value is noted. Since the NONMEM® objective function follows a χ^2 distribution, a

decrease in the objective function by ≥3.84 (P<0.05, 1 degree of freedom) units was considered to be significant for hierarchical models. At each forward addition step, the covariate that resulted in the most significant drop in objective function was retained in the model. After all the forward addition steps, a full model is developed that consists of all statistically significant covariates. The full model is then subjected to backward elimination where each covariate effect is removed sequentially. The increase in objective function between hierarchical models was assessed at a higher level of significance (P<0.001, 1 degree of freedom). A covariate was considered to be significant if its removal resulted in an increase in the objective by ≥10.83. All covariates that met this criterion were retained in the model, and the resulting model was called the final model.

Model qualification

The population pharmacokinetic model was qualified using bootstrapping and visual predictive check (VPC). A nonparametric bootstrap (n=1,000) was conducted on the final model to evaluate the stability and confidence intervals of parameter estimates.[26] The bootstrap sampling procedure was stratified based on the DISAM variable to preserve the proportions of patients with their dialysis status and the number of samples per patient (one or more than one sample). All the bootstrap runs were included irrespective of minimization status in the calculation of 95% confidence intervals of parameter estimates. Parameters lacking zero in the 95% confidence intervals were retained in the final model. A stratified VPC[19] was conducted using 1,000 simulated datasets using the final model with PsN tools. Stratification was done based on dialysis status and whether or not a patient had one concentration. The 90% prediction intervals (PI) of the simulated quartiles were visually compared with observed values by using the VPC plot in XPOSE4.

Simulation Strategy for the Evaluation of Current Nomogram Efficiency

We adopted a non-parametric approach for the definition of patient population. We utilized the same population of patients that were used in the development of population pharmacokinetic model development. Thus, the NONMEM dataset used for simulations was the original modeling dataset, but the dosing and sampling schedules were modified. The dosing regimen was created based on the current nomogram being used to dose vancomycin in Emory University hospital. The current nomogram doses patients based on CrCL and WT. Based on the patient covariate information (CrCL and WT), an appropriate dose was imputed using R software in the simulation dataset. Sampling times were imputed in the simulation dataset using R software, to represent trough concentrations after each of first 6 doses. The trough concentrations were simulated one hundred times for each subject (SUBPROBLEMS=100 in NONMEM). The proportion of subjects having trough concentrations within 10 and 20 mg/L (therapeutic range) was determined. Further, modifications to the current dosing scheme were evaluated to propose an improved dosing nomogram that increases the percentage of subjects falling within the therapeutic range in simulations. The dosing regimen was optimized by simulating trough concentrations after introducing a loading dose and iteratively modifying the maintenance dose.

RESULTS

Patient Population

Of the 1920 patients who were administered at least one dose of vancomycin, 1812 were included, with 336 (18.5%) receiving hemodialysis. Patients were excluded if the concentrations obtained were >120 hours' time post dose (TPST) or if vancomycin serum concentrations were BQL of 5 mg/L. More than half of patients were male, with a median CrCL of 62 ml/min (Table

1). There were a total of 2765 concentrations, with a median serum concentration of 18 mg/L (range: 5.1-120 mg/L). Nearly two-thirds of patients had only one concentration, but these patients represented 44% of the total concentration data points.

Population Pharmacokinetic Model Development

Vancomycin pharmacokinetics was best described by a two-compartment model (Figure 1) with drug input as a zero-order infusion. BSV parameters were estimated on total body clearance (CL), volume of distribution of central compartment (V_c), and peripheral compartment (V_p). A combined additive and proportional error model described the residual variability. Volume parameters were normalized to a 70-kg individual before other covariate relationships were examined. Covariates that were significant in the forward addition and backward elimination procedure include CrCL on CL (−1849 objective function points), DIAL on CL (−119 objective function points), and DIAL on V_c (−50 objective function points). BSV on CL was reduced to 39.8% in the final model from 76.8% in the base model. BSV on V_c marginally increased to 81.6% in the final model from 76.7% in the base model. BSV on V_p decreased to 57.1% from 290.2% in the base model. Inclusion of covariates into the model also removed the parameter-covariate correlations observed in the plots of random effects of specific parameters (etas) versus covariates in the base model. Age was a significant covariate on CL but was collinear with CrCL. Likewise, BUN was a significant covariate on CL, but it was not retained because a collinear term, CrCL, is used widely in dose calculation for vancomycin. Osmolality, potentially a surrogate for clinical volume status, was not found to be a significant covariate on V_c. The final model had a terminated minimization due to rounding errors and a successful covariance step (S-matrix calculation). Careful evaluation of output from the covariance step was conducted to

accept the results. All the correlations between parameters were <0.95 in the correlation matrix. The GOF plots for the final model are presented in Figure 2. The plots of observed concentrations versus predicted concentrations showed good agreement between observed data and predicted data. There was a trend observed in CWRES versus PRED throughout model development; the trend involved a decrease in CWRES values with increasing PRED value. This trend in the CWRES vs PRED plot was largely removed to make the CWRES values more uniformly distributed around the zero line by the final model. No trends were observed in the CWRES vs time plot. The condition number for the final model was 739, which indicates that the final model has good stability without any serious collinearity.

The stratified VPC for the final model (Figure 3) showed good agreement between the 90% prediction intervals of simulated predictions (black dashed lines) and the observed concentrations (red dashed lines). The median of simulated predictions (black solid line) and the median of the observed concentrations (red solid line) also showed good agreement. Bootstrap analysis resulted in no parameters including zero in their 95% confidence intervals (Table 2).

Simulation Strategy for the Evaluation of Current Nomogram Efficiency

A total of 181,200 subjects were simulated. In the first step, trough concentrations were simulated in accordance with the current nomogram-based dosing of vancomycin. This resulted in a mean dose of 36.2 mg/kg/day in non-dialysis subjects. For the dialysis subjects, the nomogram-based dosing resulted in a mean dose of 16.8 mg/kg/day. With the current nomogram-based dosing, 27.5% (Table 3) of subjects were in the therapeutic range at the trough after first dose. By the third dose, the proportion of subjects in therapeutic range rose to 43.6% (Table 3) but declined to 31.4% (Table 3) by the trough after sixth dose. Visual inspection of the boxplots (Figure 4a) reveals that initially the median is below the therapeutic range, which then

enters the therapeutic range and finally is outside the therapeutic range. This phenomenon is more prominent in dialysis subjects. In simulations, the additive residual error component resulted in concentrations below zero; these were excluded while plotting the boxplots.

Simulations to Optimize the Current Dosing Strategy

An iterative approach of introducing a loading dose and modifying maintenance doses was utilized to arrive at an optimized dosing nomogram. In the first iteration of simulation, a 25 mg/kg loading dose was introduced. The maintenance dose on the other hand was reduced by 30% and 50% for non-dialysis and dialysis patients, respectively. This resulted in an optimized dosing for non-dialysis patients. However, it was not optimal for the patients on dialysis. In the second iteration of simulation, maintenance dose for patients on dialysis was further reduced by an additional 10% (i.e., 60% lower than the current nomogram dosing). This resulted in more dialysis subjects falling within the therapeutic concentration range. The loading dose, however, seemed to be high for this population. In the third iteration of simulation, a 15 mg/kg loading dose, which is 40% lower than the loading dose in the previous simulation iteration, was selected. This resulted in an optimized dosing for patients on dialysis. The optimal loading dose for non-dialysis patients is therefore 25 mg/kg, whereas for dialysis patients, it is 15 mg/kg. In the optimized dosing nomogram, the maintenance dosing was reduced by 30% for non-dialysis patients and by 60% for dialysis patients as compared to the current dosing nomogram. The optimized dosing resulted in 46.7% of subjects to be in the 10-20 mg/L by the trough after the first dose (Table 3). This is substantially higher than the 27.5% achieved with the current dosing nomogram (Table 3). The percent of subjects in the 10-20 mg/L was maintained above 40% even after the trough after the sixth dose with the optimized dosing. The optimized nomogram dosing is contrasted with the current nomogram dosing at various levels of CrCL in Table 4.

DISCUSSION

We developed a robust population pharmacokinetic model of vancomycin based on real-world data from hospitalized patients, including a significant proportion that was receiving hemodialysis. The population pharmacokinetic model was subsequently used to conduct simulations to evaluate and optimize the nomogram-based dosing. Unsurprisingly, CrCL and hemodialysis status were found to be important covariates for vancomycin clearance and volume of distribution, but we found several important differences when assessing hemodialysis status. Clearance in patients undergoing hemodialysis was approximately 65% of the clearance in non-dialysis patients, and the V_c in hemodialysis patients was approximately 50% lower compared to the V_c non-dialysis patients. The steady-state volume of distribution (V_c+V_p) was 1.4 and 1.0 L/kg in the non-dialysis and dialysis patient populations, respectively. A higher steady-state volume of distribution in non-dialysis patients was observed compared to the commonly used volume of distribution estimate of 0.4-1 L/kg. This could lead to under-dosing in the initial dosing period and a longer half-life in non-dialysis patients leading to a greater-than-expected accumulation.

There is a marked effect of intermittent dialysis on clearance and volume of distribution. The volume of distribution of the central compartment was 52% higher compared to peripheral compartment in the non-dialysis patient population. With the reduction of volume distribution of central compartment in dialysis patients by 50%, the volume of distribution for the central compartment was 24% lower compared to the peripheral compartment. This shift in the ratio of volume of distribution of central to peripheral compartments due to dialysis could be explained by the fluid dynamic changes between compartments. A higher central compartment volume in non-dialysis patients is probably due to the volume overload caused by third spacing because of

the accumulation of interstitial space fluid and capillary leak in the ICU population. Intermittent hemodialysis could be normalizing the volume overload in patients by removal of the extracellular volume component resulting in a lower central compartmental volume. In hemodialysis, more fluid loss occurs from the extracellular than the intracellular compartment.[27] A similar phenomenon was reported for the pharmacokinetics of darbepoetin alfa in hemodialysis patients, where the central volume of distribution was reduced by 17% in hemodialysis patients as compared to peritoneal dialysis patients.[28]

Our findings are consistent with the published literature on population pharmacokinetic modeling[29-34] of vancomycin, though it is difficult to directly compare the results because of differences in patient populations, covariates, and differences in parameterization. The BSV parameters were higher than those reported previously, but the current dataset represents the largest patient population reported and does represent "real-world" data. In general, the BSV was high especially on volume parameters when the sample size was large in previous reports. The covariates CrCL and DIAL accounted for approximately 37% of the BSV on CL. BSV on V_c, however, increased marginally after adding DIAL as covariate. One major difference we observed was a greater central volume of distribution compared to peripheral volume of distribution in non-dialysis patients. Previous reports suggested a higher peripheral volume compared to central volume of distribution.[32-34] Several modeling approaches were attempted to confirm whether this was a numerical issue or data-driven phenomenon. They include fixing parameters to literature values, local search of parameters, constraining central volume to be lower than peripheral volume, subsetting dataset to exclude patients with only one concentration, total daily dose as a covariate on clearance to test for inherent correlations,[35] and evaluation of covariance parameters using OMEGA BLOCK structure. None of these methods provided a

better fit than the model with higher central compartment volume compared to peripheral compartment volume. A similar phenomenon was reported previously with meropenem in burn patients, where meropenem had a 70% higher central volume compared to peripheral volume in the absence of edema and 280% higher in the presence of edema.[36]

Our finding of a higher volume of distribution is in contrast to a previous study reported on the pharmacokinetics of vancomycin in patients with varying renal function (CrCL >60 ml/min, 10-60 ml/min, and <10 ml/min).[3] In this study, there were no statistical differences identified in steady-state volume of distribution in the three groups. The patient population in our dataset manifested a wide variety of disease states, and this may have caused the higher volume of distribution estimate.

It has been shown that the dosing of vancomycin using a nomogram increases the probability of achieving the target serum concentration range,[37] reduces the time spent in evaluating dosing regimens with pharmacokinetic equations, and thereby reducing expenditure.[38] A target trough concentration range of 15 to 20 mg/L has been recommended to achieve the pharmacodynamic target of the AUC/MIC≥400. We chose a trough concentration range between 10 and 20 mg/L for our simulation activity in order to include the >10-mg/L threshold based on clinical experience.

The current nomogram-based dosing is not optimal for the patient population (Table 4). The average trend in the serum concentrations shows that (Figure 4a) the majority of patients were in the sub-therapeutic range, and after multiple doses, they were in the supra-therapeutic range. This could be due to the fact that there were significant differences in the volume of distribution observed in this study compared to prior literature. Also, the current nomogram is based on a linear relationship between clearance and CrCL whereas the population pharmacokinetic model

is based on a power relationship, which will have a saturation effect. Introduction of a loading dose and maintenance dose optimized such phenomenon. The importance of introducing a loading dose in the dosing of vancomycin has been highlighted previously.[39, 11] The introduction of a loading dose is especially beneficial to rapidly achieve desired concentrations in patients with severely compromised renal function. A loading dose of 25-30 mg/kg has been recommended.[2] We chose to be conservative by selecting 25 mg/kg as a loading dose, and then in the iterative simulation exercise reduced it to 15 mg/kg in dialysis patients. It is important to note that current nomogram instructed to load with 20-25 mg/kg IV once (maximum dose 2,000 mg for trough 10-15 mg/L and 2,500 mg for trough 15-20 mg/L). However, only 24% of the first doses in the current population were above 20 mg/kg indicating this recommendation was not followed. The survey on adherence to the 2009 consensus guidelines highlights the inconsistent use of loading doses across US hospitals,[40] and our simulations demonstrate the value of consistent use of loading dose in this population.

Thomson et al. conducted a similar population pharmacokinetic modeling and simulation activity to optimize nomogram-based dosing.[39] Their nomogram was similar to ours in that it also included a loading dose. The maintenance and loading doses recommended were slightly higher than that of our optimized nomogram. They reported 71% of predicted vancomycin concentrations in the range of 10 to 20 mg/L over the first 4 days of therapy. Rapid achievement of therapeutic concentrations also is controversial in clinical practice having implications with regard to renal toxicity. The results we present here are simulated concentrations, which include the residual component of the variability, as opposed to the predicted concentrations, which do not include the residual component. The predicted concentrations from our optimized nomogram (results not shown) resulted in 89% being in the 10-20 mg/L range by the trough after the third

dose. For the dialysis patient population, our optimized nomogram-based dosing resulted in a loading dose of 15 mg/kg and a mean maintenance dose of 6.7 mg/kg/day. The loading dose value of 15 mg/kg is lower than the 20 to 25 mg/kg[41] and similar to the 15 mg/kg[42, 43] values reported previously in hemodialysis patients. The maintenance dose of 6.7 mg/kg translates to approximately 500 mg for a 70-kg person, and this value matches closely with previous reports.[42, 43] Our estimates of mean maintenance dose (25.3 mg/kg/day) in the non-dialysis patient population match closely with 27 mg/kg/day[44] reported in critically ill patients.

This study has some limitations. We obtained a convenience sample from two hospitals; our findings may not be generalized to all settings, but our sample size is larger than most studies. The time stamps for collection of vancomycin concentrations and administration of vancomycin dose may not be fully accurate due to documentation errors and variability, which may have introduced systemic error. We excluded the 3.6% of all vancomycin concentrations that were below the limit of quantitation due to numerical instability during the model development when those concentrations were included. Methodological studies showed that exclusion of such a low number (<5%) of BQLs would not bias the parameter estimation.[45] The removal of BQL data was helpful in giving numerical stability to the final model. Hemodialysis status was used as a binary variable in the covariate model. Limitations in the documentation prevented the usage of actual hemodialysis times. We could not ascertain when the patients were receiving continuous renal replacement therapy or peritoneal dialysis, though in these patients the CrCL may be an accurate reflection of vancomycin clearance. Also, given that there is not a direct causal relationship between serum vancomycin concentrations and toxicity,[2] it is unclear if the optimized nomogram will lead to fewer adverse events. A prospective validation of the optimized nomogram should be conducted before it is adopted into clinical practice.

CONCLUSION

We developed a population pharmacokinetic model for vancomycin from routinely collected critically ill patient data and found significant differences in the hemodialysis population that could inform future approaches to vancomycin dosing. The simulation activity conducted with the developed population pharmacokinetic model resulted in an optimized nomogram for dosing vancomycin. This new proposal of nomogram substantially improved the percent of subjects in the therapeutic range while introducing a loading dose and reducing the maintenance dose.

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Figure Legends

Figure 1. Two-compartment model for vancomycin pharmacokinetics

Figure 2. Basic diagnostic plots of vancomycin population pharmacokinetic model

Figure 3. Visual predictive check plot for the final model stratified on hemodialysis status and number of samples per patient.

Legend:

DISAM=1 (Non-dialysis subjects with one concentration)

DISAM=2 (Dialysis subjects with one concentration)

DISAM=3 (Non-dialysis subjects with more than one concentration)

DISAM=4 (Dialysis subjects with more than one concentration)

Figure 4A. Boxplots of the proportion of subjects in the therapeutic range following original nomogram dosing (current dosing nomogram)

Figure 4B. Boxplots of the proportion of subjects in the therapeutic range following proposed dose adjustments (optimized dosing nomogram)

Legend:

Red dashed lines indicate the target therapeutic range of vancomycin: 10 to 20 mg/L

#Table 1. Summary of the demographic and laboratory characteristics of 1812 patients included in the analysis.

Demographics/Clinical variable	Value Median [range] or Proportion
Age (years)	57 (17-101)
Male	969 (53.5%)
Weight (kg)	79 (33-255)
Hemodialysis ICU Non-ICU (ward)	336 (18.5%) 111 (33%) 225 (67%)
Intensive care unit stay during hospitalization	1172 (64.7%)
Laboratory values	
Vancomycin serum concentration (mg/L)	18 (5-120)
Number of samples vs patients	
1	1215
2	377
3	138
4	52
5	19
>5[a]	11
Creatinine (mg/dl)	1.3 (0.2-16.6)
Creatinine clearance (ml/min)	62 (4-150)
Blood urea nitrogen (mg/dl)	20 (1-198)
Osmolality (mOsm/kg)	282 (238-362)

[a] Five patients with 6 samples, four patients with 7 samples, one patient each with 9 and 12 samples.

Table 2. Results of the final population kinetics model for vancomycin in hospitalized patients.

Parameters	Values (%RSE)	1000-Sample Bootstrap	
		Median	95% Confidence Interval
CL (L/h)	4.5 (1.8)	4.5	4.3-4.7
V_c (L)	58.4 (5.1)	55.9	40.7-80.1
V_p (L)	38.4 (4.4)	40.3	29.8-50.2
Q (L/h)	6.5 (17.3)	6.8	0.9-11.7
CrCL on CL	0.8 (2.2)	0.8	0.8-0.9
DIAL on CL	0.7 (4.3)	0.7	0.6-0.7
DIAL on V_c	0.5 (12.1)	0.5	0.3-0.7
BSV on CL (%CV)	39.8 (5.0)	39.9	35.6-43.9
BSV on V_c (%CV)	81.6 (11.4)	84.4	51.3-113.9
BSV on V_p (%CV)	57.1 (23.4)	54.5	44.2-128.6
Residual Variability			
Additive Error SD (mg/L)	3.4 (3.0)	3.4	2.3-4.4
Proportional error (%CV)	22.7 (2.5)	22.6	19.2-25.4
Covariate Relationships			
$TVCL = \theta_1 \times \left(\frac{CrCL}{120}\right)^{\theta_2} \times \theta_3^{DIAL}$ $\quad$ $TVVc = \theta_4 \times \left(\frac{WT}{70}\right) \times \theta_5^{DIAL}$			
θ_1—CL; θ_2—CrCL on CL; θ_3—DIAL on CL; θ_4—V_c; θ_5—DIAL on V_c			
CrCL: creatinine clearance; CL: clearance; CV: coefficient of variation; DIAL: hemodialysis status; BSV: between-subject variability; RSE: relative standard error; Q: intercompartmental clearance; SD: standard deviation; TVCL: population mean value of clearance; TVV_c: population mean value of central volume of distribution; Vc: central volume; Vp: peripheral volume; WT: body weight			

Table 3. Percent of subjects in the therapeutic range using the current nomogram and the optimized dosing.

Troughs	Dosing	
	Current nomogram dosing	Optimized nomogram dosing
After 1st dose	27.5	46.7
After 2nd dose	44.5	48.3
After 3rd dose	43.6	48.3
After 4th dose	39.2	47.1
After 5th dose	35.0	45.4
After 6th dose	31.4	43.7

Table 4. Current dosing nomogram and optimized dosing nomogram.

Creatinine clearance (ml/min)	Dosing		
	Original dosing nomogram	Optimized dosing nomogram	
	Mean maintenance dose mg/kg/day (SD mg/kg/day)	Mean maintenance dose mg/kg/day (SD mg/kg/day)	Median loading dose (mg/kg) (range mg/kg)
≤30	12.6 (1.5)	6.7 (2.1)	15 (15-25)
31 to 60	19.6 (4.4)	12.9 (3.6)	25 (14.0-25)
60 to 90	35.1 (7.2)	23.9 (5.8)	25 (12.1-25)
91 to 120	55.1 (5.7)	38.2 (4.7)	25 (9.9-25)
121 to 150	54.5 (6.4)	37.8 (5.3)	25 (11.3-25)
>150	54.2 (7.1)	37.7 (5.3)	25 (9.8-25)