Pharmaceutical Sciences Asia

Pharm Sci Asia 2024; 51(3), 241-249
DOI:10.29090/psa.2024.03.24.AP0723

Research Article

Population Pharmacokinetic Modeling and Convenient Sampling of Midpoint Concentration for Therapeutic Drug Monitoring of Vancomycin in Vietnamese Pediatric Patients

Le Ba Hai[1], Phung Chi Kien[1], Nguyen Thi Dua[3], Nguyen Trong Hao[3], Vu Manh Hung[4], Nguyen Thanh Hai[1], Jennifer Le[2], Nguyen Thi Lien Huong[1]*

1 Department of Clinical Pharmacy, Faculty of Pharmacology and Clinical Pharmacy, Hanoi University of Pharmacy, Hanoi, Vietnam
2 Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, California, USA
3 Department of Pharmacy, Saint Paul Hospital, Hanoi, Vietnam
4 Department of Pharmacy, Thanh Hoa Pediatric Hospital, Thanh Hoa, Vietnam

ABSTRACT

(1) Background: Bayesian AUC-guided dosing of vancomycin is suggested for pediatric patients, preferably obtaining 2 concentrations with at least 1 trough concentration (ie. Peak and trough concentration - traditional sampling). However, this approach achieves optimal performance only when using a population pharmacokinetic (popPK) model of vancomycin suitable for the targeted population. Besides, obtaining 2 concentrations at the exact time in pediatrics poses challenges. This study aims to establish a popPK model of vancomycin in Vietnamese pediatric patients and explores the capability of Midpoint Concentration instead of traditional sampling; (2) Methods: This study included pediatric patients ≥ 3 months in two pediatric hospitals with a combined 2000 beds. The popPK analysis was performed by using a non-linear mixed-effect modeling approach with Monolix 2023R1®. Monte Carlo simulation was conducted using Simulx 2023R1® to explore if any Midpoint Concentration (C_{mid}) between Peak Concentration (C_{peak}) and Trough Concentration (C_{trough}) can replace traditional sampling in predicting the Area Under the Curve (AUC) of vancomycin; (3) Results and discussion: A total of 289 vancomycin concentrations from 98 patients with a median age of 1.86 [IQR 0.92 – 3.22] years, were included. The final model was as follows: CL (L/h) = 0.433*(BW/13.86)^0.777*(0.46/SCr)^0.83*(ln(age)/3.26)^2.16; and Vd (L) = 11.5*(BW/13.86)^0.777 (BW: kg, SCr: mg/dL, age: day). The internal validation demonstrated that the final model successfully described the observed data with bootstrap analysis, WRES, NPDE, and pcVPC plots showing good prediction performance. Compared to 2-point monitoring, the accuracy and precision of AUC calculating from C_{mid} were below 10% (4.6% and 5.7% respectively); (4) Conclusions: The popPK model of vancomycin in Vietnamese pediatric patients over 3 months old was well established, with body weight, age, and serum creatinine identified as significant covariates. A single concentration between peak and trough concentrations could be an feasible approach for dosing and monitoring vancomycin therapy in pediatrics.

Keywords:
Vancomycin; Vietnamese; Pediatric Patients; Population Pharmacokinetics (popPK); Midpoint Concentration

1. INTRODUCTION

For nearly 7 decades of clinical use, vancomycin has remained a crucial part of the treatment regimen for Gram-positive infections, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) in both adults and children[1,2]. However, due to increasing resistance, the therapeutic window of vancomycin has gradually

***Corresponding author:**
* Nguyen Thi Lien Huong Email: huongntl@hup.edu.vn

narrowed over time[3,4]. Pediatric patients exhibit distinct pharmacokinetic characteristics compared to adults, as vancomycin concentration can fluctuate significantly among individuals and over time[5]. Consequently, individualized dosing of vancomycin for each pediatric patient through therapeutic drug monitoring of blood concentration (TDM) assumes paramount importance and is presently conducted in hospitals globally.

The consensus recommendation from the Infection Diseases Society of America (ASHP - IDSA - PIDS - SIDP) in 2020 suggested implementing AUC-guided monitoring instead of trough-only monitoring as the previous recommendation in 2009, with area-under-the-curve over 24 hours to minimum inhibitory concentration (AUC/MIC) of 400 – 600 as the primary pharmacokinetics (PK)/ pharmacodynamics (PD) predictor[6,7]. This was the first time a consensus was reached for pediatric patients with the involvement of the Pediatric Infectious Diseases Society (PIDS), the treatment target was preferably AUC/MIC of 400 for infants and children to optimize therapeutic efficacy and minimize nephrotoxicity. In the pediatric population, the Bayesian method has also been recently endorsed by the guideline, citing advantages such as: enabling quantification at any given time without waiting for a steady state, shortening the time to reach the PK/PD target, or incorporating with patient characteristics (age, body weight, renal function, etc). However, this approach required a population pharmacokinetic (popPK) model of vancomycin characterized for the targeted population to achieve optimal performance[7].

In pediatric patients, especially critically ill patients, obtaining blood samples poses a remarkable challenge for both patients and healthcare providers[8]. The recent guideline suggested Bayesian AUC-guided dosing through traditional sampling, which included 2 concentrations, with at least 1 trough concentration (ie. Peak and trough concentration - traditional sampling)[7]. However, collecting two blood samples or one blood sample at a specific time might not always be feasible for pediatric or critically ill patients in clinical settings[9]. The risk of anemia and adverse events may increase for pediatric patients undergoing repeated blood draws, especially those associated with low hemoglobin levels or blood volume depletion[10]. Therefore, the one-concentration approach with flexible sampling times could serve as a potential solution for pediatric patients for both feasibility and economic reasons.

The objective of our study was to establish a population pharmacokinetics model of vancomycin characterized for Vietnamese pediatric patients and explore the capability of the Midpoint Concentration strategy instead of traditional sampling.

2. MATERIALS AND METHODS

2.1. Study design

This prospective cohort study was conducted at Thanh Hoa Pediatric Hospital and Saint Paul General Hospital with a combined 2000 beds. Patient records were identified and analyzed prospectively from 2022 to 2023. The study included data from patients aged between 3 months and 16 years who indicated Therapeutic Drug Monitoring (TDM) services from April 1, 2022 to April 2, 2023. Patients with a history of renal replacement treatment, hemodialysis, peritoneal dialysis, or extracorporeal membrane oxygenation were excluded from the study. Additionally, patients with inaccessible medical records or missing information regarding dosing and sample collection times were also excluded.

2.2. Vancomycin administration and data collection

The initial dosing regimen for vancomycin, determined by the physician, ranged from 40 to 80 mg/kg/day, divided into 2 to 4 doses based on the severity and type of infection. Vancomycin was administered via intravenous infusion over 1 to 2 hours. Dosage adjustment was based on vancomycin TDM results. In our study, the sampling time was determined under the consensus reached between the doctors and clinical pharmacists, considering the combination with other biochemistry tests to minimize the number of blood samples. The concentrations obtained during the TDM process were classified into 3 groups according to the timing of the blood sample:

- C_{peak}: 1 – 2 hour after the end of infusion
- C_{trough}: 0,5 – 1 hour before the next dose
- C_{mid}: randomized concentration between peak and trough concentration

In addition to collecting vancomycin levels, we gathered data on each patient's age, gender, weight, height, hematocrit, albumin, and serum creatinine. The patient's eGFR was calculated by the Schwartz equation, as follows[11]:

$$\text{eGFR (mL/min/1,73m}^2\text{)} = k^* \times \frac{\text{Height (cm)}}{\text{Creatinine serum (mg/dL)}}$$

*k = 0.45 with patients from 3 months – 1 year old; k = 0.4 with patients from 1 – 16 years old

2.3. Bioanalytical method for determination of vancomycin

Vancomycin concentrations in all subjects were determined by hospital laboratory assays available at

each site. The serum concentration of vancomycin at Thanh Hoa Pediatric Hospital was measured by the kinetic interaction of microparticles in a solution (COBAS 701, Roche), the linear range for the assay was 4 – 80 mcg/mL with the limit of quantitation was 4 mcg/mL. At Saint Paul General Hospital, drug concentrations were determined by using a validated chemiluminescent microparticle immunoassay (ARCHITECT i2000SR, Abbott Laboratories, Abbott Park, IL), with the assay range from 1.1 – 100.0 mcg/mL (limit of quantitation was 1.1 mcg/mL), the intraday and the interday coefficient of variations were less than 10%.

2.4. Population PK modeling

The popPK parameters were carried out using the nonlinear mixed effects modeling approach using the Monolix 2023R1 software with Stochastic Approximation Expectation Maximization (SAEM). To identify the appropriate structural model, we investigated the 1- and 2-compartment model with the parameter clearance (CL) and volume of distribution (Vd). The inter-individual variability (IIV) model characterized the random variability in the pharmacokinetic parameters were assumed to be log-normally distributed. Residual unexplained variability was tested with an additive, proportional, and combined (additive and proportional). The model selection was based on corrected Bayesian information criterion (BICc) value, 2 × log-likelihood reduction (objective function; OFV), and goodness of fit (GOF) plots. The percentage of the relative standard error (R.S.E) was considered as a measure of parameter precision.

We assessed the effects of age, actual body weight, SCr, eGFR calculated by the Schwartz equation as continuous covariates, and gender as categorical covariates. The covariate modeling was based on a stepwise approach, each covariate was added to the model one at a time. For stepwise forward addition, a covariate would be significant if its addition led to a decline in the OFV of at least 6.635. A covariate was retained in the model if a covariate removal increased OFV more than 10.828 ($p<0.001$) for stepwise backward elimination.

2.5. Model evaluation

In the model evaluation procedure, visual inspection of goodness-of-fit (GOF) plots such as individual predicted concentration against observed concentration, individual weighted residuals (IWRES) against time and individual predictions, the normalized prediction distribution errors (NPDE), and prediction-corrected visual predictive checks (pcVPC) were carried out. Prediction correction aims to correct for the differences within a bin coming from independent variables (time, dose, and other covariate values) in the model and hence more clearly diagnose model misspecification in both fixed and random effects. Therefore, the pcVPC had an enhanced ability to diagnose model misspecification, especially with respect to random effects models in a range of situations. The nonparametric bootstrapping (500 data sets) resampling procedure was conducted to evaluate the stability and robustness of the final popPK model.

2.6. Exploring convenient sampling of midpoint concentration

The popPK parameters from the final model were also used to explore whether any randomized Cmid between C_{peak} and C_{trough} can replace traditional sampling in predicting the Area Under the Curve (AUC) of vancomycin. We defined 3 strategies based on the number and sampling time of vancomycin serum concentrations:

- Mid-only: Obtained only one midpoint concentration.
- Trough-only: Obtained only one trough concentration.
- 2-point: Obtained 2 concentrations, with at least one trough concentration.

After processing the Monte Carlo simulation 1000 times with Simulx 2023R1®, we assessed the precision and accuracy of the Mid-only monitoring compared to the 2-point strategy or Trough-only strategy. Accuracy referred to the extent of systematic error, indicating whether a parameter is consistently over- or under-predicted. Precision, on the other hand, denoted the random error, indicating the level of variation in estimation.

Accuracy, defined as median % predicter error:

$$\sum \frac{(X_{estimated} - X_{actual})}{X_{actual}}$$

Precision, defined as median % predicted absolute error:

$$\sum \frac{(|X_{estimated} - X_{actual}|)}{X_{actual}}$$

The value for the $X_{estimated}$ was AUC derived from the Mid-only sampling strategy and the values for the X_{actual} were AUC derived from the 2-point or Trough-only strategy. If the accuracy and precision were less than 10%, it was considered acceptable.

Table 1. Patient Demographics and Clinical Data

Characteristics	Values N = 98
Male, n (%)	55 (56.12)
Age, years	1.86 (0.92 – 3.22)*
Weight, kg	10.75 (8.00 – 15.00)*
Height, cm	91.07 (72.00 – 102.00)*
Baseline Serum creatinine, mg/dL	0.51 (0.4 – 0.53)*
ICU admission, n (%)	75 (76.53)
Infections	
Pneumonia, n (%)	75 (76.53)
Blood infections, n (%)	32 (32.65)
Skin and soft tissue infections, n (%)	2 (2.04)
Intracranial infection, n (%)	4 (4.08)
Septic arthritis, n (%)	3 (3.06)
Vancomycin initial dose, mg/kg	60.0 (57.14 – 61.31)*

*Data expressed in Median (interquartile range/IQR)

3. RESULTS

3.1. Demographics

A total of 98 Vietnamese pediatric patients with 289 vancomycin concentrations were included in the study. The median age was 1.86 (interquartile range [IQR] 0.92 – 3.22) years old, body weight 10.75 (IQR 8.00 – 15.00) kg, baseline serum creatinine 0.51 (IQR 0.4 - 0.53) mg/dL and empiric dose 60.0 (IQR 57.14 – 61.31) mg/kg/day. Most subjects were admitted to the ICU unit (76.53%) and received empiric vancomycin for pneumonia (76.53%), and bacteremia (32.65%). Summary of patient demographic and clinical characteristics is presented in Table 1.

A total of 289 serum vancomycin concentrations were analyzed (Table 2). The vancomycin concentration was widely distributed over the dosing interval, including 36 samples of peak concentrations, 108 middle concentrations, and 145 samples were measured as trough concentrations. Median peak, middle, and trough concentrations were 19.93 mcg/mL, 17.24 mcg/mL, and 8.245 mcg/mL, respectively. According to clinical practice, vancomycin dosages for pediatric patients were adjusted based on renal function and therapeutic drug monitoring results.

3.2. Population PK model

The base model was a one-compartment pharmacokinetic with linear elimination as it outperformed the two-compartment model. The pharmacokinetic parameters such as Vd and CL were estimated with the proportional error model, which best described the residual unexplained variability in this pediatric population. The stepwise covariate analysis identified body weight on both clearance and volume of distribution, creatinine serum, and age on clearance as model significant parameter-covariate, with the BICc value was 1773.45. The inclusion of covariates in the final model decreased the intersubject variability from 64.8% to 35% for clearance and from 35.1% to 25.2% for Vd.

Table 2. Vancomycin Concentration

Vancomycin concentration	Values N = 289
Peak Concentration	
Number, n(%)	36 (12.46)
Concentration, mcg/mL	19.93 (4.16 – 50.13)+
Time after dose, hour	2.01 (1.77 – 3.07)+
Midpoint Concentration	
Number, n(%)	108 (37.37)
Concentration, mcg/mL	17.24 (4.44 – 43.81)+
Time after dose, hour	3.00 (2 – 5)+
Trough Concentration	
Number, n(%)	145 (50.17)
Concentration, mcg/mL	8.245 (1.82 – 29.55)+
Time after dose, hour	5.00 (4 – 8.12)+

+Data expressed in Median (minimum-maximum)

Table 3. Population pharmacokinetic parameter estimates of the vancomycin final model and bootstrap parameters

	Estimates	R.S.E (%)	Bootstrap N=500
Population parameters			
Θ_1	11.5	7.02	11.5 (9.89 – 13.47)*
Θ_2	0.433	4.92	0.49 (0.38 – 0.72)*
Effect of body weight on Vd, CL	0.777	10.2	0.80 (0.65 – 0.97)*
Effect of Creatinine Serum on CL	0.83	4.68	0.89 (0.54 – 1.26)*
Effect of age on CL	2.16	1.24	1.98 (1.50 – 2.32)*
IIV (%)			
IIV_Vd (%)	25.2	41	27.2 (15.96 – 40.38)*
IIV_CL (%)	35	10	33.11 (25.79 – 39.52)*
Residual error	0.327	5.78	0.32 (0.28 – 0.36)*

*Data expressed in Median (interquartile range/IQR)

Abbreviation: *Vd: volume of distribution; CL: clearance; IIV: Inter-individual Variability R.S.E: Relative standard error*

The pharmacokinetic parameters of the final model are presented in Table 3. The R.S.E for the inter-individual variability values for all parameters were below 50%, indicating good precision. The individual models for the volume of distribution (Vd) and clearance (CL) for a typical individual are represented by Eqs. 1 and 2, respectively.

Equation:

$$(1)\ Vd\ (L) = 11.5 * \left(\frac{BW}{13.86}\right)^{0.777}$$

$$(2)\ CL\ (L/h) = 0.433 * \left(\frac{BW}{13.86}\right)^{0.777} * \left(\frac{0.46}{Scr}\right)^{0.83} * \left(\frac{ln(age)}{3.26}\right)^{2.16}$$

Abbreviation: *Vd: volume of distribution; CL: clearance; BW: actual body weight in kg; SCr: actual creatinine serum in mg/dL; Age: actual age in day*

3.3. Model evaluation

The GOF plots for the internal validation are described in Figure 1, individual predicted values were densely distributed along the symmetry line. The IWRES were randomly distributed around zero, with most of the individual weighted residuals within the range of − 2 to 2.

The parameters estimated in the bootstrap analysis are presented in Table 3. All the pharmacokinetic parameter values were within the 95% confidence interval of bootstrap results, and 100% of replicates were successful.

The pcVPC plot of the simulation demonstrated that 90% prediction interval included most of the detection values, indicating good predictive performance of the final model (Figure 2). The

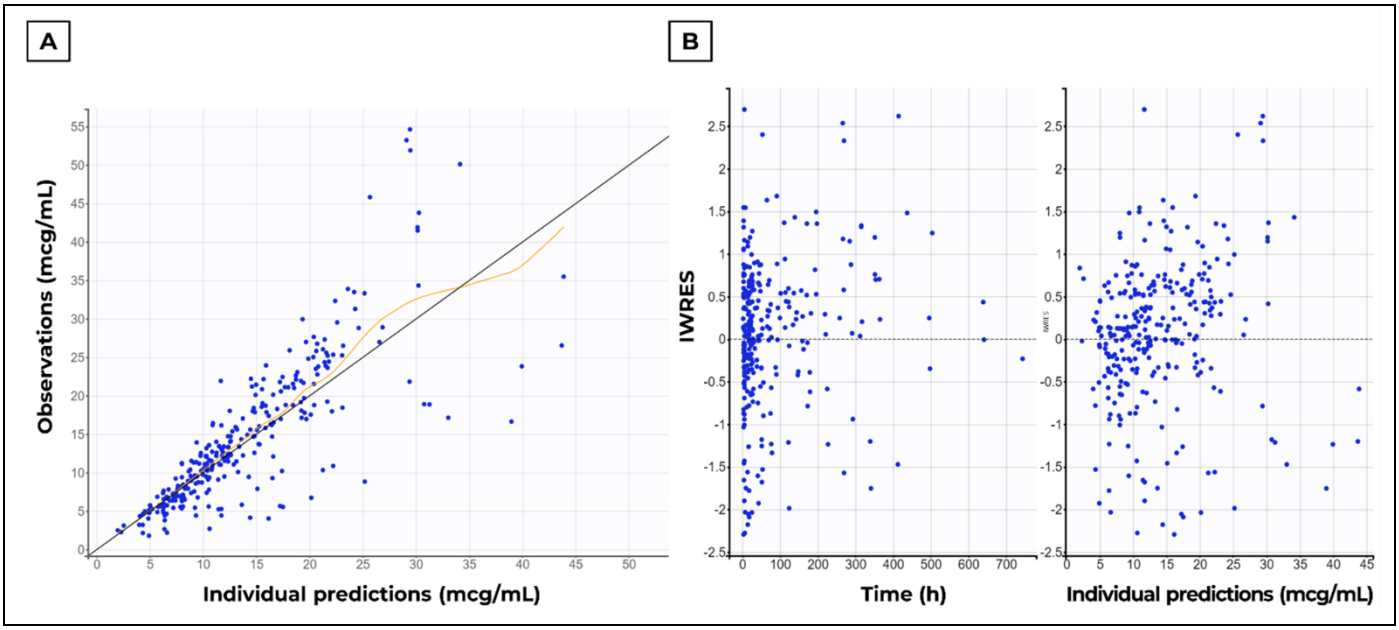

Figure 1. (A) Observed vancomycin concentrations versus individual predictions; (B) Individual weighted residuals (IWRES) versus time and individual predictions

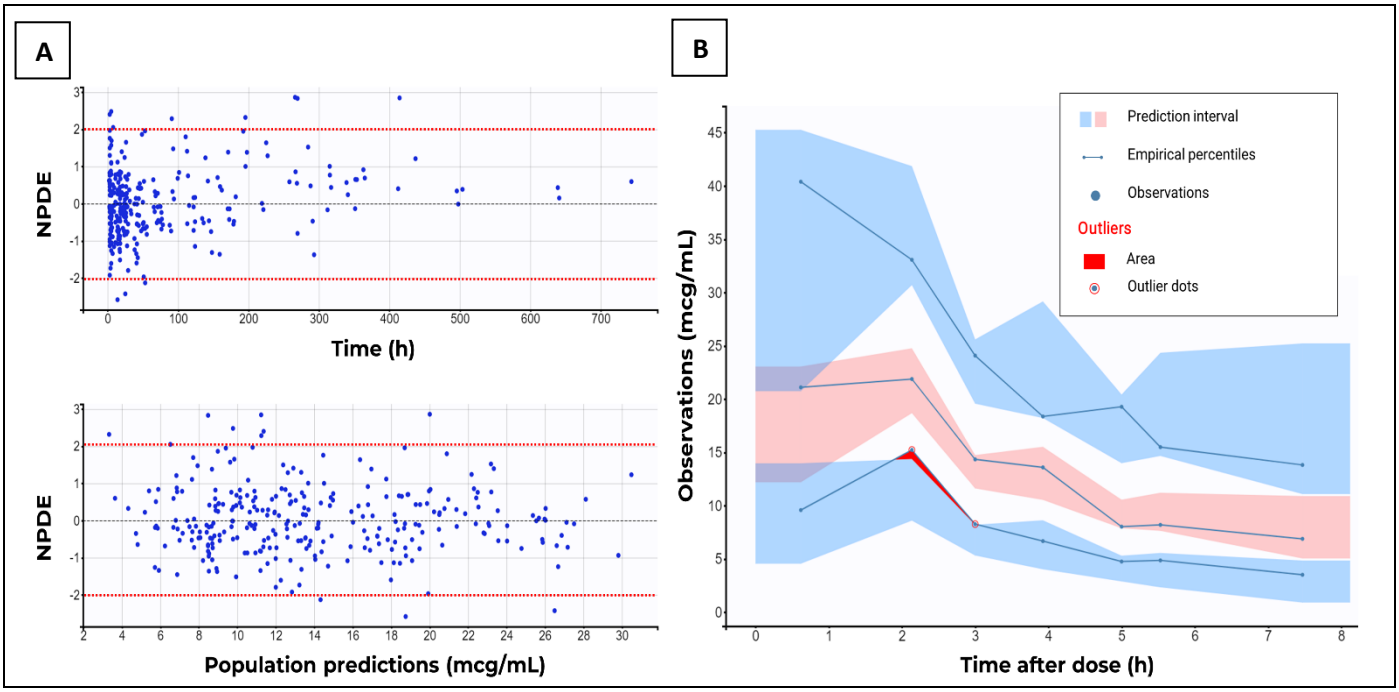

Figure 2. (A) The normalized prediction distribution errors (NPDE); (B) Prediction-corrected visual predictive checks (pcVPC)

numerical NPDE results mostly ranged from -2 to 2, exhibited good accuracy and stability, and yielded excellent fits to predict individual and popPK parameters.

The shrinkage values of individual parameters (CL, Vd) were below 10%, indicating that individual estimates closely align with observed data for that individual, implying greater confidence in the estimates provided by the final model (Figure 3).

3.4. Evaluating a limited blood sampling strategy

Compared to the 2-point monitoring, the accuracy and precision of AUC calculated by the Mid-only monitoring were 4.6% and 5.7%, respectively. When contrasted with Trough-only monitoring, utilizing Mid-only monitoring for calculating AUC resulted in the accuracy of 6.9% and the precision of 8.5% (Figure 4**)**. We also assessed the systematic differences between the two methods of estimating AUC (Mid-only versus 2-point or Trough-only) as well as the variability of the differences via the Bland-Altman plot (Figure 5), the majority of differences were within the limits of agreement, which were set at the mean difference ± 1.96 standard deviations of the differences.

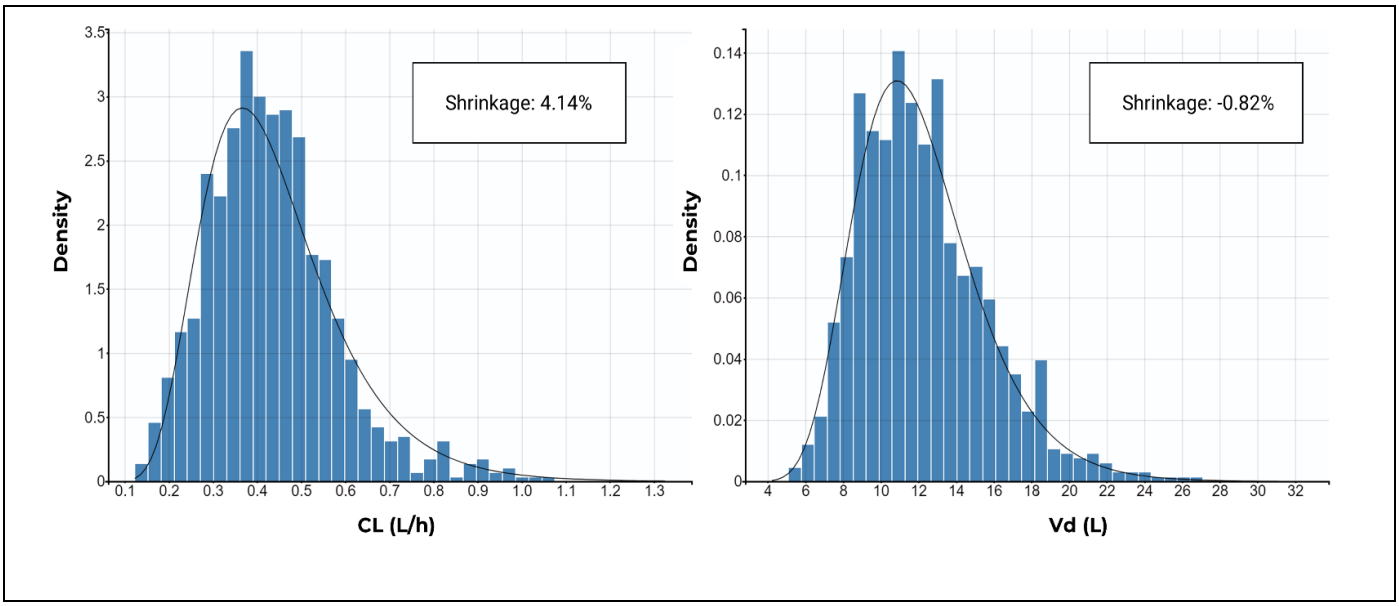

Figure 3. Distribution of the individual parameters

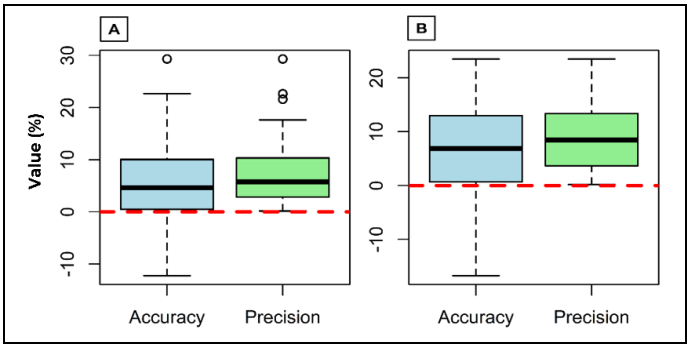

Figure 4. (A) Accuracy and precision of AUC calculated by Mid-only strategy versus 2-point strategy, (B) Accuracy and precision of AUC calculated by Mid-only strategy versus Trough-only strategy

4. DICUSSION

With the sampling time widely distributed over the dosing interval, our dataset could comprehensively cover all the pharmacokinetics phases of vancomycin,allowing us to reliably determine the popPK parameters of our pediatric patients. The concentration data analysis indicated that the one-compartment model with intravenous administration and first-order elimination was the most suitable model to describe vancomycin concentration data of Vietnamese pediatric patients above 3 months old. This finding was consistent with the majority of previous studies that used a one-compartment model to describe vancomycin pharmacokinetic parameters[12].

In our final model, the values of CL and Vd after weight adjustment were 0.136 L/kg/h and 0.878 L/kg, respectively. To our knowledge, this is the first published popPK model of vancomycin for Vietnamese pediatric patients so comparisons with other studies conducted in Vietnam have not yet been feasible. However, compared to the previous studies in the world about the popPK model for the pediatric population, the results of CL and Vd were within the reported range, with CL ranging from 0.014 L/kg/h to 0.27 L/kg/h (median 0.082 L/kg/h) and Vd ranging from 0.43 L/kg to 1.46 L/kg (median 0.6 L/kg). The study by Le et al. in the largest pediatric patient population (n = 702) demonstrated non-significant differences in CL parameters compared to our research, with CL after weight adjustment were 0.121 L/kg/h[13]. Our estimated Vd was slightly greater than Vd in the study of Le (0.878 L/kg versus 0.636 L/kg), because our pediatric population, with a median age of 1.86 years old, was significantly younger than subjects in Le's study, which had a median age of 6.6 years old[13]. The Vd indicated that it would decline along with the increase in the age of children[14,15].

The final popPK model verified similar results as most of the references: body weight, age, and serum creatinine concentration as important covariates for CL and body weight as an important covariate for Vd[12]. However, a study by Lu et al. on the population of patients with a wide age distribution (9.36 ± 4.59 years old) and a research by Moffet et al. including a wide range of age groups (30.1% neonates, 30.1% of infants, 24.7% of children and 15.1% of adolescents) indicated age was an important covariate along with weight that affected Vd[16,17]. Meanwhile, in our study, the effect of age on Vd had not been reported, because the age of our population was not widely distributed with mostly from 3 months to 2 years old (54.08%).

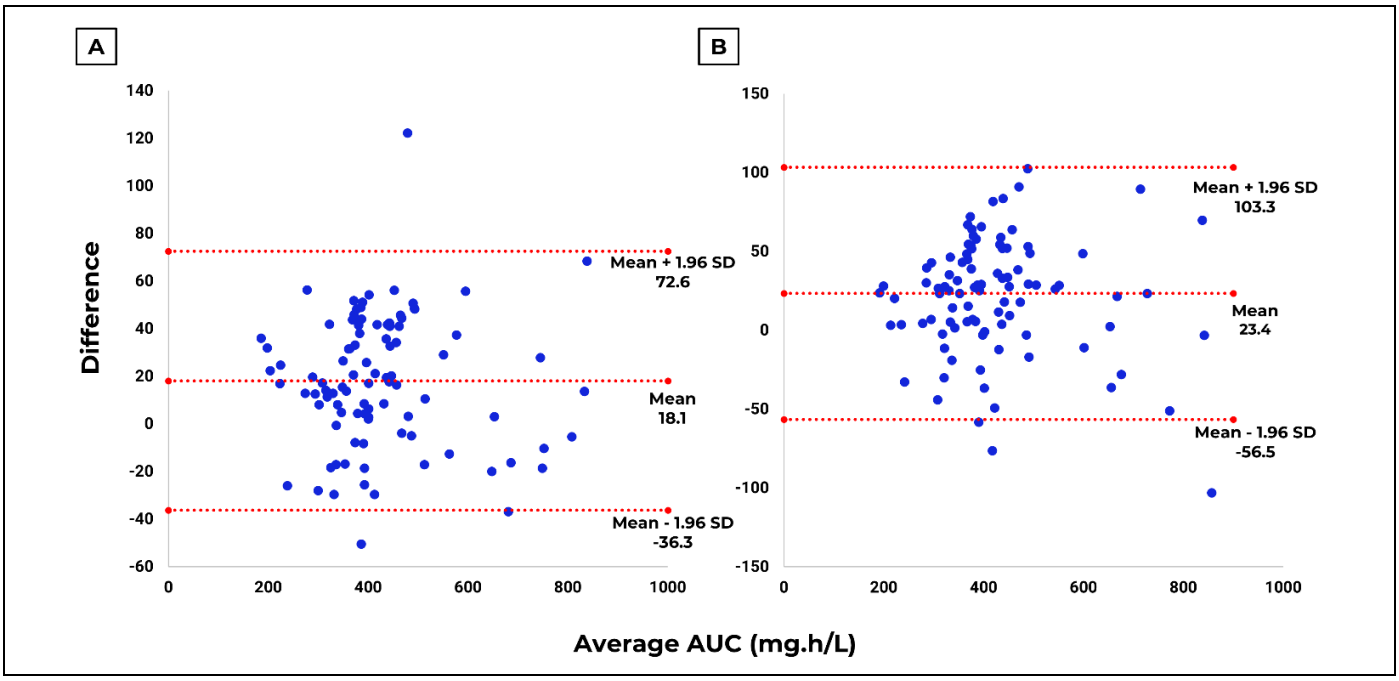

Figure 5. (A) Bland Altman plot of AUC calculated by Mid_only versus 2_point; (B) Bland Altman plot of AUC calculated by Mid_only versus Trough_only

Bayesian-guided dosing involed a process wherein the initial probability distribution of a patient's pharmacokinetic parameter values prior to drug administration (known as the Bayesian prior) was refined based on precise dosing and drug concentration data to generate an updated probability distribution (referred to as the Bayesian conditional posterior). In essence, employing an apporiate popPK model tailored to targeted population cohort in conjuction with individual patient information allowed precise dosing regimens. Moreover, this methodology was computable at any temporal juncture and enabled prediction with minimal blood samples[18,19]. Many studies in pediatric patients were undertaken to investigate the feasibility of employing one-concentration blood sampling regimens in predicting AUC via the Bayesian method, with the majority of these single-point blood sampling regimes focused on trough concentration[20-23]. However, the findings across studies remained controversial, with certain perspectives advocating for the inclusion of additional peak concentration to enhance predictive accuracy[20,23]. Hence, we embarked on an exploration to determine whether a blood sampling regimen at any point between the peak and trough concentrations could have been precise and accuracy enough for practical implementation.

Utilizing the final popPK model and executing the Monte Carlo simulation 1000 times, we found that no significant difference between the Mid-only and 2-point or Trough-only strategies when estimating AUC by the Bayesian approach (both accuracy and precision were below 10%). These results could be explained by the understanding that peak concentrations generally represented the volume of distribution, while trough concentrations indicated the clearance[24]. Therefore, one concentration between peak and trough concentrations held the potential to effectively signify both volumes of distribution and clearance.

The consensus guidelines in 2020 suggested Bayesian AUC-guided dosing and monitoring for pediatric patients, mostly based on adult data, and proposed a monitoring strategy involving 2 concentrations with at least 1 trough concentration[7]. However, in clinical practice, precise timing for blood sampling poses a significant for physicians, in particular, the trough concentration collection (30 minutes to 1 hour before the next dose). The midpoint sampling strategy could be an approach that beneficial for healthcare workers. Its broader time frame allowed for better coordination with other laboratory sampling routines, enhancing overall efficiency. This approach not only enhances medication monitoring but also has the potential to reduce costs. Moreover, it improves patient convenience by minimizing the number of blood concentrations, while also reducing the work burden for healthcare providers.

There were some limitations, which need to be addressed in future studies. External validation was not conducted, so we will proceed with collecting additional data from new patients to perform this in the next phase. The results will help confirm the predictive ability of the developed model, as well as the effectiveness of the convenient sampling strategy.

In other hand, we concurrently developed the open–source software for Model-Informed Precision Dosing (MIPD), integrating our final popPK model. The software is now availabe at: https://tdmvanco.shinyapps.io/PCKdemo/. This free program with an intuitive interface and support for the Vietnamese language is expected to promote widespread implementation of vancomycin therapeutic drug monitoring targeting AUC in hospitals across middle-income countries like Vietnam.

5. CONCLUSION

The population pharmacokinetics model of vancomycin in Vietnamese pediatric patients over 3 months old was well established, with body weight, age, and serum creatinine identified as significant covariates. A single concentration between peak and trough concentrations could be an feasible approach for dosing and monitoring vancomycin therapy in pediatrics.

6. ACKNOWLEDGMENT

Conflict of interest
The authors declare that they have no conflict of interest.

Funding
This research received no external funding

Ethics approval
This research was reviewed and approved by the Ethical Committee, under the approval number 629/QĐ-BVĐKXP and 939/QĐ-BVN.

Article info:
Received May 17, 2024
Accepted June 25, 2024

REFERENCES

1. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 2014; 59(2): e10-52.
2. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clinical infectious diseases:

an official publication of the Infectious Diseases Society of America 2011; 52(3): e18-55.
3. Hughes JH, Tong DMH, Lucas SS, Faldasz JD, Goswami S, Keizer RJ. Continuous learning in model-informed precision dosing: a case study in pediatric dosing of vancomycin. Clinical pharmacology and therapeutics 2021; 109(1): 233-42.
4. Rubinstein E, Keynan Y. Vancomycin revisited - 60 years later. Front Public Health 2014; 2: 217.
5. Shoji K, Saito J, Nakamura H, Matsumoto K, Oda K, Takesue Y, et al. Current aspects of pediatric pharmacokinetics and pharmacodynamics of antimicrobials in Japan: Importance of the promotion of population PK/PD analysis. Pediatr Infect Dis J 2022; 41(10): e418-e23.
6. Rybak M, Lomaestro B, Rotschafer JC, Moellering R, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. American Journal of Health-System Pharmacy 2009; 66(1): 82-98.
7. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. American journal of health-system pharmacy: AJHP: official journal of the American Society of Health-System Pharmacists 2020; 77(11): 835-64.
8. Ravindranath TM, Baird JS. Obtaining blood cultures in critically ill children: The need for a cultural change. Pediatric critical care medicine: a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2020; 21(1): 107-8.
9. Le J, Bradley JS. Optimizing antibiotic drug therapy in pediatrics: current state and future needs. Journal of clinical pharmacology 2018; 58 Suppl 10: S108-s22.
10. Peplow C, Assfalg R, Beyerlein A, Hasford J, Bonifacio E, Ziegler AG. Blood draws up to 3% of blood volume in clinical trials are safe in children. Acta paediatrica (Oslo, Norway : 1992) 2019; 108(5): 940-4.
11. Schwartz GJ, Haycock GB, Edelmann CM, Jr., Spitzer A. A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976; 58(2): 259-63.
12. Chung E, Sen J, Patel P, Seto W. Population pharmacokinetic models of vancomycin in paediatric patients: A systematic review. Clinical pharmacokinetics 2021; 60(8): 985-1001.
13. Le J, Bradley JS, Murray W, Romanowski GL, Tran TT, Nguyen N, et al. Improved vancomycin dosing in children using area under the curve exposure. Pediatr Infect Dis J 2013; 32(4): e155-63.
14. Eidelman C, Abdel-Rahman SM. Pharmacokinetic considerations when prescribing in children. 2016; 1(1): 69-80.
15. Batchelor HK, Marriott JF. Paediatric pharmacokinetics: key considerations. Br J Clin Pharmacol 2015; 79(3): 395-404.
16. Moffett BS, Morris J, Galati M, Munoz F, Arikan AA. Population Pharmacokinetics of vancomycin in pediatric extracorporeal membrane oxygenation. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2018; 19(10): 973-80.
17. Lu JJ, Chen M, Lv CL, Zhang R, Lu H, Cheng DH, et al. A population pharmacokinetics model for vancomycin dosage optimization based on serum cystatin C. European journal of drug metabolism and pharmacokinetics 2020; 45(4): 535-46.
18. Jelliffe RW, Schumitzky A. Modeling, adaptive control, and optimal drug therapy. Medical progress through technology 1990; 16(1-2): 95-110.
19. Bayard DS, Jelliffe RW. A Bayesian approach to tracking patients having changing pharmacokinetic parameters. Journal of pharmacokinetics and pharmacodynamics 2004; 31(1): 75-107.
20. Le J, Ngu B, Bradley JS, Murray W, Nguyen A, Nguyen L, et al. Vancomycin monitoring in children using bayesian estimation. Therapeutic drug monitoring 2014; 36(4): 510-8.
21. Stockmann C, Olson J, Rashid J, Lubsch L, Young DC, Hersh AL, et al. An evaluation of vancomycin area under the curve estimation methods for children treated for acute pulmonary exacerbations of cystic fibrosis due to methicillin-resistant *Staphylococcus aureus*. Journal of clinical pharmacology 2019; 59(2): 198-205.
22. Ho D, Arquiette J, Kim MK. Bayesian-estimated vancomycin area under the curve using a single trough concentration vs 2 concentrations. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 2021; 78(18): 1663-4.
23. Kim HK, Jeong TD. Evaluation of vancomycin area under the concentration-time curve predictive performance using bayesian modeling software with and without peak concentration: an academic hospital experience for adult patients without renal impairment. Annals of laboratory medicine 2023; 43(6): 554-64.
24. Hedaya, M.A. Basic Pharmacokinetics 3rd ed: Routledge; 2023.