ORIGINAL ARTICLE

The association between vancomycin trough concentrations and nephrotoxicity in the paediatric intensive care unit

A associação entre concentrações no vale de vancomicina e nefrotoxicidade em uma unidade de terapia intensiva pediátrica

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ABSTRACT

Objective: To analyze and describe the pharmacokinetic aspects of vancomycin usage in a cohort of critically ill children and to construct a pharmacokinetic model for this population. **Method:** We conducted an observational study in a pediatric intensive care unit from September 2017 to March 2019. Children receiving vancomycin with at least one serum measurement were included. Variables with a p-value lower than 0.2 in univariate analysis, and biologically plausible for inducing nephrotoxicity and not correlated with other predictors, were incorporated into logistic regression. Additionally, pharmacokinetic modeling was performed using the PMETRICS® package for patients with creatinine clearance (CLCR) > 30 mL/min. **Result:** The study included 70 children, with an average vancomycin dose of 60 mg/kg/day. Only eleven children achieved vancomycin levels within the target range (15-20 mg/L). No significant differences in doses/mg/kg/day were observed among children above, within, or below the vancomycin target range. In the multivariate model, children above the recommended serum range had an odds ratio of 4.6 [95% CI 1.4 – 17.2] for nephrotoxicity. A pharmacokinetic model was proposed using data from 15 children, estimating PK parameters for CLCR and V as 0.94 L/h and 5.71 L, respectively. **Conclusion:** Nephrotoxicity was associated with vancomycin plasma concentrations equal to or exceeding 15 mg/L. The developed model enhanced understanding of the drug's behavior within this population, potentially aiding clinical practice in dose calculations and estimation of the area under the curve – a recommended parameter for vancomycin monitoring.

RESUMO

Objetivo: Analisar e descrever os aspectos farmacocinéticos do uso de vancomicina em uma coorte de crianças sob cuidados intensivos e elaborar um modelo farmacocinético para essa população. **Método:** Estudo observacional em uma unidade de terapia intensiva pediátrica conduzido entre setembro de 2017 a março de 2019. Inclui-se crianças em uso de vancomicina com pelo menos uma mensuração sérica desse antimicrobiano. As variáveis com valor de p < 0,2 na análise univariada e com plausibilidade biológica para propiciar nefrotoxicidade, não correlacionadas com outras preditoras, foram incluídas na regressão logística. Adicionalmente, uma modelagem farmacocinética foi realizada usando o programa PMETRICS® para pacientes com *clearance* de creatinina (CLCR) > 30 mL/min. **Resultado:** Foram incluídas 70 crianças no estudo. A dose média de vancomicina foi de 60 mg/kg/dia. Apenas onze crianças apresentaram vancocinemia dentro da faixa alvo (15-20 mg/L). Não foram observadas diferenças significativas entre as doses administradas e a observação de vancocinemia acima, dentro ou abaixo da faixa preconizada. No modelo multivariado, crianças acima da faixa sérica preconizada apresentaram *odd ratio* de 4,6 [IC 95% 1,4 – 17,2] para nefrotoxicidade. Um modelo farmacocinético com os dados de 15 crianças foi proposto, no qual os parâmetros de PK estimados para CLCR e Volume de distribuição foram de 0,94 L/h e 5,71 L, respectivamente. **Conclusão:** A nefrotoxicidade mostrou-se associada às concentrações plasmáticas de vancomicina iguais ou maiores a 15 mg/L. O modelo desenvolvido permitiu entender o comportamento do fármaco nessa população e pode ser útil na prática clínica para o monitoramento do uso de vancomicina.

INTRODUCTION

Vancomycin is a glycopeptide antimicrobial used to treat serious infections, including those triggered by methicillin-resistant *Staphylococcus aureus* (MRSA)[1]. In Brazil, MRSA infections are more prevalent in pediatric intensive care units (PICUs) than in other countries[2], resulting in a potential increase in the use of this glycopeptide in children under intensive care[1]. The clinical context influences the pharmacokinetic parameters of vancomycin, mainly due to changes in protein binding, extracellular volume and renal elimination[3]. In pediatric patients treated with vancomycin, there is a faster clearance and a reduced half-life compared to adults[4]. Consequently, regular monitoring of serum vancomycin levels is crucial to ensure both the efficacy and safety of treatment[5].

The detection of minimum plasma vancomycin concentrations (vancomycin serum trough concentrations) equal to or greater than 15 mg/L represents a risk factor for the development of nephrotoxicity in children[6]. On the other hand, insufficient plasma levels of vancomycin are directly linked to ineffective treatment, the multidrug resistanc emergence e and, in extreme cases, death[7].

Over the last few years, the criteria for monitoring vancomycin`s use have been revised. Initially focused on obtaining minimum plasma concentrations, or trough concentrations, in the target range of between 15 and 20 mg/L (for serious infections in pediatric patients), it has been modified to calculate the area under the curve (AUC) under the minimum inhibitory concentration (MIC), to estimate total exposure to the drug, expected to be between 400 and 600 mg[8]. However, this approach requires at least two measurements of vancokinemia and involves calculations of a slightly more complex nature[9]. As a result, it is common for many hospitals to rely on plasma trough concentrations values when monitoring[10].

Regarding intraindividual and interindividual variability in pharmacokinetic (PK) and pharmacodynamic (PD) processes in children[11,12], population PK modeling (popPK) is an analytical technique that is increasingly being used to determine optimal dosing regimens[13]. However, there is a lack of studies to characterize popPK parameters in vulnerable subgroups of children, such as dialysis patients[13].

Our study aimed to correlate data on minimum plasma concentrations of vancomycin with the occurrence of nephrotoxicity and to develop a model for describing pharmacokinetic parameters in a cohort of critically ill children and adolescents admitted to a university pediatric hospital.

METHODS

Study design, location and participants

We conducted an observational study with retrospective data collection in the PICU of a university pediatric hospital located in Rio de Janeiro, Brazil. The PICU had ten beds, six of which were for pediatric patients, three for newborns undergoing surgical procedures, and one isolation bed.

The inclusion criteria were: (i) patients admitted to the ICU between September 2017 and March 2019, which corresponds to an interval of 18 months; (ii) age range between 0 and 18 years; (iii) vancomycin use for a period of more than 48 h; (iv) performance of at least one vancokinemia test at the time of lowest concentration (voucher).

Patients who underwent multiple courses of vancomycin treatment during their hospital stay were treated as separate individuals in the data analysis process. Patients were followed up until they were discharged from the PICU or died. No exclusion criteria were applied.

Sources of information and definition of variables

We collected data from records in various sources of information at the institution. These sources included the patients' physical medical records, electronic drug prescriptions, laboratory information available in the hospital programs PAGU and PSSD (MV 2000®, Recife, PE), as well as the case progress documents recorded by the clinical pharmacy service.

In the process of characterizing the patient cohort, we considered key variables such as age (expressed in years), weight (measured in kilograms), biological sex, and the presence of comorbidities. The stratification of children into distinct age groups adhered to the guidelines recommended by the World Health Organization[14].

The treatment and monitoring protocol for vancomycin`s use was based on a guideline established by the hospital under investigation, aimed at critically ill pediatric patients with an indication for this antibiotic therapy[15]. The antibiotic was administered intravenously using an infusion pump and lasted between 30 minutes and one hour. As outlined in the guideline, venous blood samples should be taken between 0 and 30 minutes before the infusion of the fourth dose, thus ensuring that the steady-state plasma concentration is obtained. The VITROS 5.1 FS equipment was used to quantify the concentration of vancomycin in human serum and plasma. The analysis was carried out on 3 µl of a blood sample, using the two-point kinetic test, following the instructions for use of the equipment and the VITROS TM Chemistry Products kit manual, issued by the Pediatric Laboratory Medicine department at the Hospital for Sick Children (SickKids).

The target therapeutic range was set between 15-20 mg/L, according to the guidelines for the population studied[15]. Patients were categorized into three groups (below, within and above the range) based on this criterion, considering the first vancokinemia collection.

Drugs with nephrotoxic potential were determined according to a list of drugs with an indicated risk of increasing nephrotoxicity when used in conjunction with vancomycin. These drugs were described in the drug interactions section available in the WHO Model Formulary for Children[16]. Previous nephropathy was defined as chronic kidney disease prior to exposure to vancomycin. The evaluation of the occurrence of nephrotoxicity and other adverse events related to vancomycin was carried out on the basis of medical reports recorded in the patients' medical records, covering the period from 24 h after the start of treatment to 72 h after the end of vancomycin administration. The literature suggests that exposure to vancomycin for less than 48 to 72 h is unlikely to trigger nephrotoxicity[6]. Time one (T1) was defined as the first plasma dose obtained after the stationary stage in the vancomycin treatment course.

Analysis

For the categorical variables, absolute and relative frequencies were presented and the comparison was made using the chi-square test or Fisher's exact test, depending on the distribution of the groups. Concerning continuous variables,, comparisons were made using the Mann-Whitney test or the Kruskal-Wallis test. The results were expressed as median and interquartile range, or mean and standard deviation. If the p-values were lower than 0.05 in the analysis with three groups, a post-hoc test was carried out, such as the Bonferroni test for continuous variables, in order to control for type I error.

Subsequently, a multivariate logistic regression model was developed to analyze the outcome of nephrotoxicity. Only variables with a p-value < 0.2 in the univariate analysis were included in the model. Independent variables that were highly correlated with each other and/or had no biological plausibility with the outcome under study were excluded from the multivariate analysis. Treatment time with vancomycin was categorized as greater than seven days for inclusion in the logistic regression model[6]. The models generated by logistic regression were subjected to diagnostic tests in order to select the best-fitting model. The Area Under the Curve (AUC) of the receiver operator characteristic (ROC) curve was calculated between the values predicted by the models generated and the observed values. In addition, Akaike's Information Criterion (AIC) and Schwarz's Bayesian Criterion (BIC) were evaluated.

We constructed a ROC curve to assess the relationship between serum vancomycin levels and the occurrence of nephrotoxicity. The cut-off point on the ROC curve was determined using the Youden test in order to determine the best balance between sensitivity and specificity. An analysis using the confusion matrix to evaluate the performance of the ROC curve in predicting nephrotoxicity based on serum vancomycin levels. The confusion matrix was constructed with true positive, true negative, false positive and false negative values. From this, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of the model were calculated using the "caret" package. P-values of < 0.05 were considered statistically significant. Statistical analyses were carried out using the epiR, stats and pROC packages in the RStudio software.

The population pharmacokinetic model was developed and validated using the PMETRICS® 1.9.7 package in RStudio (version 1.3.1056). Due to the number of patients included, it was decided to design a one-compartment model using the non-parametric adaptive grid (NPAG) algorithms. Vancomycin excretion from the central compartment was modeled as a linear process and the residual error as gamma * (1 + 0.1*concentration), value = 5^{17}.

The clinical covariates were analyzed for biological plausibility and then the covariate analysis was carried out, testing linear, log, polynomial and power regression for the continuous variables. The linear model was used to analyze the categorical variables, and the covariates were related to pharmacokinetic parameters. The covariates available in the database, such as gender, age, weight, body mass index, serum creatinine and estimated creatinine clearance (eCLC) were the parameters chosen for testing in the structural model.

The model was evaluated using diagnostic figures to compare and select the models. Firstly, a visual analysis was made of the relationship between the observed and simulated concentrations in each race, making adjustments where necessary. In addition, the linear regression of the observed and predicted values was analyzed (R-squared

closer to 1, intercept closer to 0, slope closer to 1, bias and imprecision smaller.

The methods were also compared using the log-likelihood ratio test (-2*LL), AIC and BIC criteria. The covariates were introduced separately into the model and tested statistically. If the inclusion of the covariate resulted in an improvement in the 2*LL, AIC or BIC values, the covariate was used in the final model.

Finally, for validation, normalized prediction error distribution (NPDE) plots were used to evaluate the predictive verification of the posterior data and the proportion of simulated observations between the 5% and 95% percentiles above 90% was considered adequate.

Ethical issues

The project was approved by the institution's Research Ethics Committee under the registration number 5.156.179.

RESULTS

The study included 70 patients, totaling 309 measurements of vancomycin`s plasma concentration. Forty-four children were male (62.9%). Their ages ranged from 12 days to 15 years, with a median of 2 years. Most of the children (84%) had at least one pre-existing medical condition. Pneumonia stood out as the main cause of hospitalization and the predominant indication for the use of vancomycin (33%), followed by sepsis (30%). Before starting vancomycin, 12 children already had a history of kidney disease. The prescribed dose of vancomycin was 60 mg/kg/day, and there were no statistically significant differences between the doses in the different groups (as shown in Table 1).

Table 1 also details the distribution of clinical characteristics according to the different categories of plasma concentration of vancokinemia at the first measurement (T1): below 15 mg/L, within the therapeutic range recommended for severe patients (15-20 mg/L) and above 20 mg/L (Table 1). It was observed that the majority of children in the group with concentrations above the indicated therapeutic range reported cases of nephrotoxicity (65.2%), as well as those within the recommended therapeutic range (72.7%) (Table 1).

There was a significantly higher frequency of nephrotoxicity in the groups with concentrations above and within the therapeutic range, compared to patients below the range, and this difference was statistically significant (p = 0.002).

Table 2 shows the comparison between the clinical characteristics and the occurrence of nephrotoxicity recorded in the medical records during the course of treatment with vancomycin, which corresponded to 45.7% of all the children monitored.

Table 3 shows the factors associated with the development of nephrotoxicity in the population investigated. Children whose vancomycin plasma concentrations at the first measurement (T1) were above the expected therapeutic range were 4.59 times more likely to develop nephrotoxicity compared to those whose concentrations were within or below the recommended therapeutic range. However, it is essential to point out that the wide confidence interval (95% CI 1.38 - 17.21) suggests considerable variability in estimating the contribution of this variable to the outcome. Figure 1 shows the ROC curve, with a cut-off point set at 14.6 mg/L to distinguish between those who did or did not have nephrotoxicity. Evaluation of the confusion matrix revealed that the ROC curve model for predicting nephrotoxicity based on vancomycin levels showed an accuracy of 71.4%. The Kappa value was 0.43,

Table 1 – Characterization of the study population and stratification according to adequacy to the recommended range of vancokinemia (15-20 mg/L) at the first collection.

Variable n (%) or median [Interquartile range]	Total	Upper	Adequate	Lower	p-value
	n = 70	n = 23	n = 11	n = 36	
Age (years)					0.657
< 1	13 (18.6)	5 (21.7)	3 (27.3)	5 (13.9)	
2-3	22 (31.4)	6 (26.1)	4 (36.4)	12 (33.3)	
3-6	16 (22.9)	6 (26.1)	1 (9.1)	9 (25.0)	
7-12	14 (20.0)	3 (13.0)	2 (18.2)	9 (25.0)	
13-15	5 (7.1)	3 (13.0)	1 (9.1)	1 (2.8)	
Weight (kg)	11.0 [6.0-16.4]	11.0 [8.2-18.9]	5.9 [4.2- 10.0]	11.9 [8.2- 15.8]	0.083
Male gender	44 (62.9)	14 (60.9)	11 (72.7)	22 (61.1)	0.762
Nephrotoxicity	32 (45.7)	15 (65.2)	8 (72.7)	9 (25.0)	0.002*
Sepsis	21 (30.0)	7 (30.4)	5 (45.5)	9 (25.0)	0.431
Nephropathy	12 (17.1)	5 (21.7)	4 (36.4)	3 (8.3)	0.075
Dose mg/kg/day	60.0 [58.2-61.0]	60.0 [55.3- 60.0]	60.5 [58.0- 61.7]	60.0 [59.7-60.9]	0.260

mg: milligrams. kg: kilogram. Continuous variables, expressed as medians and interquartile ranges, were compared using the Kruskal-Wallis test. Categorical variables were expressed as relative and absolute frequencies and were compared using the chi-square test or Fisher's exact test, when more appropriate. *Post hoc tests were applied to variables with a p-value < 0.005.

Table 2 – Stratification between the occurrence of nephrotoxicity, N = 70.

Variable n (%) or median [interquartile range]	Nephrotoxicity		p-value
	Yes	No	
	n = 32	n = 38	
Age (years)			0,209
< 1	5 (15.6)	8 (21.1)	
2-3	7 (21.9)	15 (39.5)	
3-6	11 (34.4)	5 (13.2)	
7-12	6 (18.8)	8 (21.1)	
13-15	3 (9.4)	2 (5.3)	
Weight (kg)	11.0 [5.8- 18.3]	11.11 [6.3- 14.5]	
Male Gender	22 (57.9)	22 (68.8)	0.491
Sepsis	16 (50.0)	5 (13.2)	0.002
Previous nephropathy	9 (28.1)	3 (7.9)	0.055
Dose mg/kg/day	60.0 [55.5- 61.0]	60.0 [60.0- 61.0]	0.187
Suitability for the vancomycin range			0.002
Upper	15 (46.9)	8 (21.1)	
Adequate	8 (25.0)	3 (7.9)	
Lower	9 (28.1)	27 (71.1)	
Time of vancomycin use in days	9.5 [6.0-17.8]	7.00 [3.3-11.5]	0.027
Nephrotoxic medication	30 (93.8)	20 (52.6)	<0.001

Continuous variables were expressed as medians and interquartile ranges and were compared using the Kruskal Wallis test. Categorical variables were expressed as relative and absolute frequencies and were compared using the chi-square test or Fisher's exact test, when more appropriate.

Table 3 – Multivariate logistic regression model using nephrotoxicity as the outcome.

Predictor variable	Odds ratio	95%CI	p-value
Time on vancomycin greater than 7 days	3.69	1.14-13.70	0.037*
Sepsis	8.42	2.41-35.38	0.001*
Serum vancomycin concentration above the recommended range at T1	4.59	1.38-17.21	0.017*
Previous nephropathy	4.89	1.03 -30.38	0.060

CI: confidence interval. *Statistically significant.
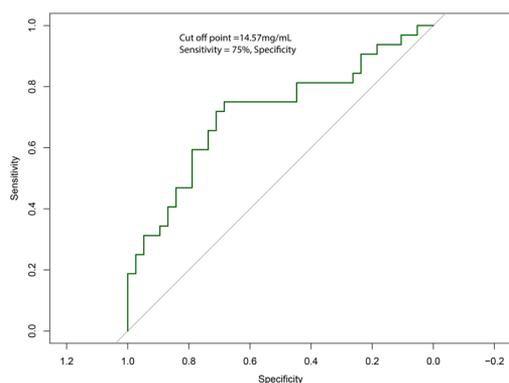
Figure 1 - Receiver Operating Characteristic (ROC) curve discriminatory for the occurrence of nephrotoxicity considering vancokinemia N =70.

indicating moderate performance. The model showed a sensitivity of 75% and specificity of 68.4%. The positive and negative predictive values were 66.7% and 76.5%, respectively. Balanced accuracy was calculated at 71.7%, showing a balance between the model's ability to identify positive and negative cases of nephrotoxicity.

Although nephrotoxic drugs have been shown to be a factor associated with nephrotoxicity (as shown in Table 2), their inclusion in the multivariate regression led to a less precise model fit, and we opted for the regression model with the highest AUC (0.81) with the results shown in Table 3.

Of the 70 patients, 15 were included in the pharmacokinetic modeling analysis because they had CLCR > 30 mL/min. This subgroup had a mean age of 2.5 years with a standard deviation (SD) of 0.5 years. Only 5 (33.3%) were female. The average weight observed
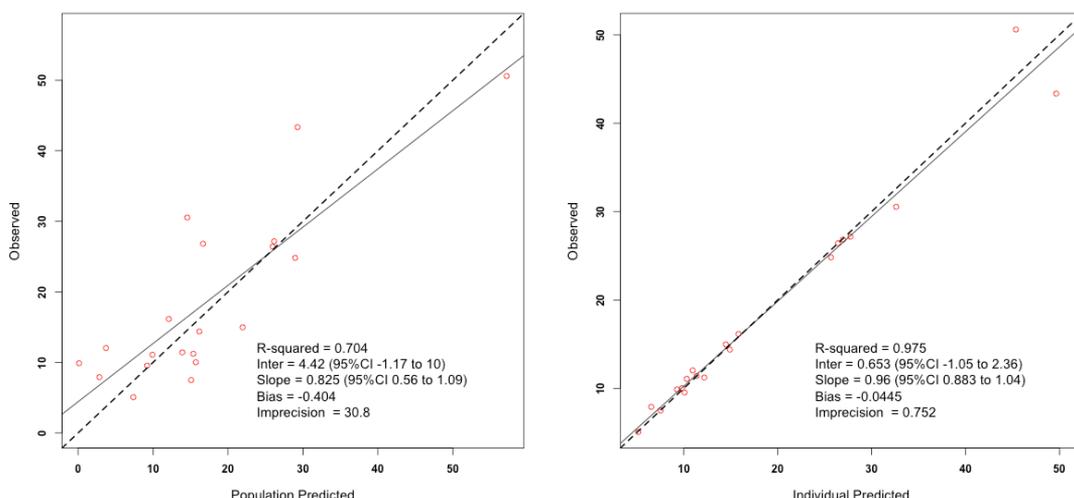
Figure 2 - Linear correlation between plasma concentration observed versus predicted by population and individual models of vancomycin in pediatric critically ill patients. N=15 patients.

was 16.6 kg (SD 5.6 kg). The estimated PK parameters for CLCR and volume of distribution (Vd) were 0.94 L/h (median = 0.91 and SD = 0.23) and 5.71 L (median = 4.27 and SD = 0.23).

During the construction of the pharmacokinetic model, it was found that the inclusion of the covariates weight normalized by 14 kg and serum creatinine by 0.287mg/dL significantly improved the model (Δ-2LL: -35.9; ΔAIC: -35.9; ΔBIC: -35.9). The linear correlation coefficient between the values obtained and those simulated (r2) was 0.704 for the population model, with a slope of 0.825 (95% CI 0.56 - 1.09) (Figure 2).

Figure 3 shows the correlation between the intervals obtained by pharmacokinetic modeling and the observed data, with few outliers.

DISCUSSION

Most of the children monitored had vancokinemia levels below those recommended in the institutional protocol. This finding is in line with another study carried out in Brazil, in which the median vancokinemia in critically ill children was 10 mg/L, considering an initial dose of 57.7 mg/kg/day[18]. Some research highlights the importance of higher doses for specific groups of patients, such as those with an increased glomerular filtration rate, in order to achieve plasma concentrations within the therapeutic range for the treatment of serious infections[19,20]. However, it is important to note that vancomycin is a drug that is subject to a number of dose-dependent adverse events[21].

This study identified a notably higher incidence of nephrotoxicity within the investigated population compared to other studies involving pediatric cohorts.. A recent systematic review found an 11.8% rate of vancomycin-related acute kidney injury in hospitalized children[22]. This figure is similar to that found in a Brazilian study carried out in pediatric intensive care[18]. However, disparities in reported incidence rates could be attributed to variations
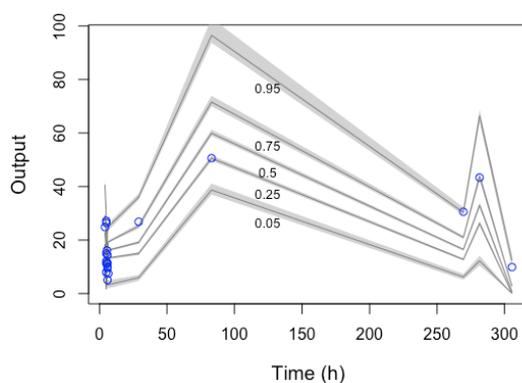
Figure 3 - Visual weighted figure of concentration versus time, VPC (visual predictive check). N=15 patients. The circles in blue are the observed concentrations (Y) over time (X) distributed in percentiles.

in inclusion criteria and definitions of nephrotoxicity across different studies.. Some researchers chose to exclude patients with a history of renal failure when selecting the sample[18]. In this study, the classification of nephrotoxicity covered cases reported in medical records, following clinical criteria established by the PICU team, which could include indicators such as laboratory tests and reduced urine output, among others. In contrast, other studies adopted stricter criteria based on laboratory test results, such as an increase of ≥0.5 mg/dL or ≥50% in relation to the baseline serum creatinine concentration[10,20,22].

Nephrotoxicity was more frequently observed among patients whose plasma concentrations were within or above the recommended therapeutic range. This result was similar to that obtained in other studies[20,23]. The literature suggests that serum levels between 15-20 mg/L, although effective, can result in an AUC/CIM greater than 400, which increases

the incidence of nephrotoxicity[9]. It is therefore crucial that institutional protocols adapt to the new vancomycin monitoring parameters to ensure patient safety[24].

Other factors associated with nephrotoxicity observed in this study, such as treatment time and sepsis, are already well documented in the literature[18,20,23]. However, several studies have presented contradictory results regarding the relationship between the duration of vancomycin therapy and the risk of nephrotoxicity[6]. While some studies have not found a significant correlation[25,26], others showed a more frequent tendency towards positive results[22,23]. The findings of the present study suggest that the length of exposure to vancomycin was a risk factor for the occurrence of nephrotoxicity, indicating the need to discontinue the use of the antimicrobial as soon as as safe from an infection poin of view, aiming to benefit the patient.

Despite the uniformity in the prescription of vancomycin in the population examined, most of the children included did not have a plasma concentration at the first dose within the range recommended in the institution's protocol. This suggests that additional factors, besides the dose of vancomycin, played a role in determining the plasma levels of this drug. The pharmacokinetics of vancomycin in children in intensive care is profoundly impacted by variations in the volume of distribution, glomerular filtration rate and the availability of plasma protein for binding[3].

Although two-compartment models have considerable advantages, it is interesting to note that around 70% of studies involving population pharmacokinetic models of vancomycin in pediatric patients have opted to use a single-compartment model[13]. In addition, one-compartment models containing at least one pair of peak and trough data per patient offer the clinical accuracy needed to predict AUC[27].

A systematic review of 64 observational studies found a wide range of clearance and Vd values (range 0.014-0.27 L/kg/h and 0.43-1.46 L/kg, respectively) with inter-individual variability of up to 49.7% for clearance and 136% for Vd. The most significant covariates for clearance were weight, age and serum creatinine or creatinine clearance and weight for Vd[13]. It is important to note that the proposed model includes all these covariates. The CLCR and Vd ranges of the children included in the modeling are in line with data previously described for pediatric populations[13,28]. Considering the R^2 values observed, the pharmacokinetic model built in this study has satisfactory predictive capacity for determining clinically individualized dosage regimens in a vulnerable group such as children in intensive care. Furthermore, inserting the model into appropriate software would enable more accurate calculation of the AUC[29,30].

The study`s findings highlight the need to re-evaluate plasma vancomycin monitoring strategies, suggesting that the emphasis on trough values may not be the safest approach for children in intensive care units exposed to this antimicrobial. Thereby, it is recommended that institutional protocols be updated to incorporate monitoring guidelines based on the AUC parameter, in order to ensure a more accurate and safer approach.

The model obtained offers an advance in understanding the pharmacokinetics of vancomycin in a pediatric population under intensive care. A previous study by Silveira et al. (2022) presented a pharmacokinetic model with data from a sample of ten Brazilian children hospitalized in a ward[29]. Considering that studies with real-life data in pediatric patients under intensive care are scarce, it is believed that the model obtained in the present investigation has the potential for practical application for pharmacokinetic calculations in patients undergoing treatment with vancomycin, by providing a more solid basis for individualized clinical decisions and could be incorporated into software for dose adjustment and calculation of AUC in patients with CLCR >30mL/min.

However, in addition to the limited number of patients included in the pharmacokinetic modeling, this analysis has other limitations, such as the lack of information on the covariates height and body surface area, and the definition of nephrotoxicity based on medical reports in medical records. Therefore, further studies are still needed.

CONCLUSION

The results of this study suggest a high incidence of nephrotoxicity associated with vancomycin, compared to other findings in the literature. The detection of vancokinemia levels above 20mg/L at the very first measurement emerged as an independent risk factor for nephrotoxicity. However, it was observed that a threshold of around 15 mg/L of serum vancomycin, in line with institutional recommendations, seems to be associated with the occurrence of nephrotoxicity.

The model developed allowed us to understand the behavior of the drug in this population and may be useful in clinical practice for monitoring the use of vancomycin

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