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Article

Vancomycin population pharmacokinetic modeling in children using Bayesian estimation and a Non Parametric Approach

Anna Luísa Oliveira Silveira[1], Geisa Cristina da Silva Alves[1], Jiao Xie[2], Jason A Roberts[2, 3, 4, 5], Cristina Sanches[1]

[1]Federal University of São João del-Rei, Minas Gerais, Brazil,, [2]The University of Queensland Centre for Clinical Research, The University of Queensland, Brisbane, Australia, [3]Department of Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Australia, [4]Pharmacy Department, Royal Brisbane and Women's Hospital, Brisbane, Australia, [5]Centre for Translational Anti-infective Pharmacodynamics, School of Pharmacy, The University of Queensland, Brisbane, Queensland, Australia

To analyze microbiological effectiveness of vancomycin in children from a pediatric hospital through population pharmacokinetic modelling, as well as to propose dose adjustment, a cross-sectional study was performed in children under vancomycin treatment from the John Paul II Children's Hospital, MG. In order to establish a model, concentrations versus time curves were analyzed using a population pharmacokinetic approach with Pmetrics®**.** Seventeen blood samples of 10 patients were collected. The best model to describe vancomycin population pharmacokinetic (PK) consisted of a two-compartment linear intravenous absorption model. The R^2 value and bias for population and individuals in observed versus predicted plot was 0.642 vs. 0.992 and the bias of 0.41 mg/L and 0.0778 mg/L, respectively. The covariables creatinine clearance, age, and body mass index were related to vancomycin PK. A relevant PK variability for vancomycin in pediatric patients was verified, which was significantly influenced by creatinine clearance, age, and body mass index. This result justifies the formulation of dosing recommendations for vancomycin in pediatric patients to achieve adequate pharmacodynamics targets.

Key-words: Glycopeptide. Vancomycin. Pharmacokinetics. Pharmacokinetic Modelling. Pediatric.

INTRODUCTION

Vancomycin is classified as a glycopeptide antibiotic with activity predominantly against Gram-positive bacteria,. Known since 1956, it is the drug of choice in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections both in adult and pediatric populations, despite its ototoxic and nephrotoxic effects (Liu *et al.,* 2011). Previous reports have demonstrated that for adults and serious susceptible MRSA infections, a vancomycin exposure target of area-under-the-curve of the serum concentrations vs. time over 24 h to minimum inhibitory concentration (AUC/MIC) ratio ≥ 400 improves treatment success, which correlates to trough concentrations between 15 and 20 mcg/mL (Rybak *et al*., 2009; Kullar *et al.,* 2012; Dalton *et al.,* 2020).

To optimize vancomycin exposure, current Infectious Diseases Society of America (IDSA) guidelines recommend vancomycin of 60 mg/kg/day empirically for treating suspected serious MRSA infections in children. In Brazil, the empirical dose usually used to treat these infections is 40 mg/kg/day (Liu *et al*., 2011; Hoang *et al*., 2014). A large population-based pharmacokinetic (PK) study in pediatric patients demonstrated that a vancomycin dose of 60 to 70 mg/kg/day was necessary, depending on age, SCr, and MIC distribution to achieve the therapeutic

***Correspondence:** C. Sanches, Universidade Federal de São João del-Rei, Campus Centro-Oeste Dona Lindu, Av. Sebastião Gonçalves Coelho, 400, CEP 35.501-296, Chanadour, Divinópolis, MG, Brazil, Phone: +55 (37) 3690-4489, E-mail: csanches@ufsj.edu.br, Anna Luísa Oliveira Silveira ORCID: 0000-0002-2061-2405

target of AUC/MIC ≥ 400 (Le *et al*., 2013). However, available data for vancomycin dosing in children is still scarce (Alves *et al*., 2017)

Although European and North American guidelines provide an excellent reference for the treatment of MRSA infections, the ideal would be to guide this therapy by local factors, including the probable sources of infection and the risk factors associated with the patient. Additionally, to guide the empirical choice of initial antibiotic therapy, as well as to make it easier for adequate treatment, updated epidemiological data on the local incidence of pathogens and resistant strains, as well as a precise microbiological diagnosis and antibiotic susceptibility tests are necessary. Therefore the present study sought to analyze vancomycin microbiological effectiveness in children from a local pediatric hospital, through population pharmacokinetic modelling.

MATERIAL AND METHODS

Setting

This was a cross-sectional PK study conducted at the John Paul II Children's Hospital (HIJPII/FHEMIG, 2016) between April 2016 and December 2016.

Ethics

Ethics approval was obtained from the Ethics Committee of the Hospital Foundation of Minas Gerais (approval reference number: 3388/22712016) and from the local Ethics Committee of the Federal University of São João del Rei (approval reference number: 1,422,909), both in March 2016. Informed consent was obtained from all participants included in the study. Children and legal guardians were invited to participate and to sign the Written Informed Consent and Term of assent. All procedures were in accordance with the Helsinki Declaration and with the 466/2012 resolution.

Study population

The inclusion criteria were: age between 2 and 12 years and antibiotic treatment with vancomycin for at least five biological half-lives (steady-state). Exclusion criteria were: renal replacement therapy patients and/or burns patients.

Dosing, administration, and data collection

Vancomycin dosing was at the physician's discretion according to the recommendations of the local Hospital Infection Control Committee. Antibiotic infusion was performed by infusion pump or micro drops.

Clinical and demographic data included age, gender, weight, height, body mass index, admission, admission unity, treatment, antibiotic infusion time, culture results, minimum inhibitory concentration, surgeries, drains, central and peripheral venous catheters, intra-arterial puncture, catheterization, naso-orotracheal intubation, and main exams. Height and BMI, when not available in medical records, were estimated from the values of anthropometric data available at the National Center for Health Statistics from the Centers for Disease Control and Prevention (CDC, 2017), where the data are estimated according to the age of each child and compared with the table of weight and height from NCHS 77/8 of the Brazilian pediatric society. Additionally, renal clearance (ClCr) was calculated trough the Schwartz *et al*. (1976) equation, which applies a constant related to age and gender; pharmacokinetic parameters of volume of distribution (V), elimination constant ratio (Kel), and drug clearance (Cl) were calculated by the model.

Sample collection, handling, storage, and measurement

Respecting the period of five half-lives to reach steady-state, two blood samples were taken from a venous catheter and / or arterial catheter (2 mL / collection in Vacutainer / Sodium EDTA bottle), with a minimal interval of 2 h for each patient. Blood samples were centrifuged (Centrifuge Excelsa Baby® I 206) within 15 minutes at 3500 rpm. The plasma supernatant (500 µl) was transferred to an eppendorf tapered tube with a 10 % solution (500 µl) of MOPS (3- [N-morpholino] -propanesulfonic acid, J.T.Baker®) and stored at -80 ºC until analysis, not exceeding six months. Samples were

analyzed by high performance liquid chromatography (HPLC) according to Alves, Chequer and Sanches (2019).

Population PK modelling

In order to develop a model, one- and two-compartment models were tested in the Nonparametric Adaptive Grid algorithm with Pmetrics®, a package for R® (Los Angeles, CA, USA). Lambda and Gamma error models were tested for inclusion. Additionally, demographic and clinical characteristics, such as weight, age, gender (male), serum creatinine, intensive care unit, creatinine clearance, and body mass index, for affecting vancomycin pharmacokinetics were also tested for inclusion as covariates when they lead to any improvement in the coefficient of determination of linear regression (R^2), or also in a reduction of the bias of the goodness-of-fit plots, as well as in a statistically significant reduction in log-likelihood ($P<0.05$). A similar analysis was performed for each run, where those same parameters were taken into account for the goodness-of-fit evaluation.

Model diagnostics

To evaluate the predictive performance, mean bias-adjusted squared prediction error (imprecision) and the bias of the population and individual prediction models were analyzed. Visual predictive check plot and the normalized prediction distribution errors, as well as weighted residual plots versus time and concentration were used to test the suitability of the final covariate model.

RESULTS

Demographic and clinical data

Ten patients fulfilled the inclusion criteria and accepted to participate in this study. 17 samples from 10 patients were measured. The study population was predominantly male (70 %) with a mean age of 7 years and did not have any observed form of renal dysfunction. The median weight was 21, 15.5-24,0 (IQ) Kg and height was 112.5 (median) 95-133 (IQ) cm. Most participants were allocated to the intensive care unit (ICU) 6 (60 %). The morbidities related to children's hospitalization were community pneumonia (30 %), cystic fibrosis (20 %), bacterial pneumonia (10 %), pulmonary sepsis (10 %), bacterial meningitis (10 %), craniotomy (10 %), and septic shock (10 %). Most were using vancomycin, empirical dose, and in four cases (40 %) in association with meropenem (Table I).

TABLE I - Demographic and clinical data

Parameter	Value
Weight (Kg)	21 (15.5 – 24.0)
Age (years)	7
Male	8 (72.72 %)
Height (cm)	112.5 (95-.0 – 133.0)
SCr (mg/dL)	0.35 (0.17)
ICU	6 (60 %)
ClCr (mL/min)	233.14 (110.64)
BMI (kg/m²)	17.02 (4.74)
Comorbidities	10 (100 %)
Pneumonia	3 (30 %)
Cystic Fibrosis	2 (20 %)
Bacterial Pneumonia	1 (10 %)
Pulmonary Sepsis	1 (10 %)
Bacterial Meningitis	1 (10 %)
Craniotomy	1 (10 %)
Septic Shock	1 (10 %)

Dichotomous variables were presented as n (%). Parametric continuous variables expressed by median (IQ) and mean (SD). Serum Creatinine; Intensive Care Unit; Creatinine clearance calculated using the Schwartz *et al.* (1976) equation; Body Mass Index.

Pharmacokinetic model building

Based on the model building, the best model consisted of a two-compartment linear intravenous absorption model with an additive error to describe the concentration–time data of the total plasma concentrations of vancomycin. The R^2 value and bias for population and individuals in observed versus predicted plot was 0.642 vs. 0.992 and the bias of 0.41 mg/L and 0.0778 mg/L, respectively (Figure 1 (A), (B)).

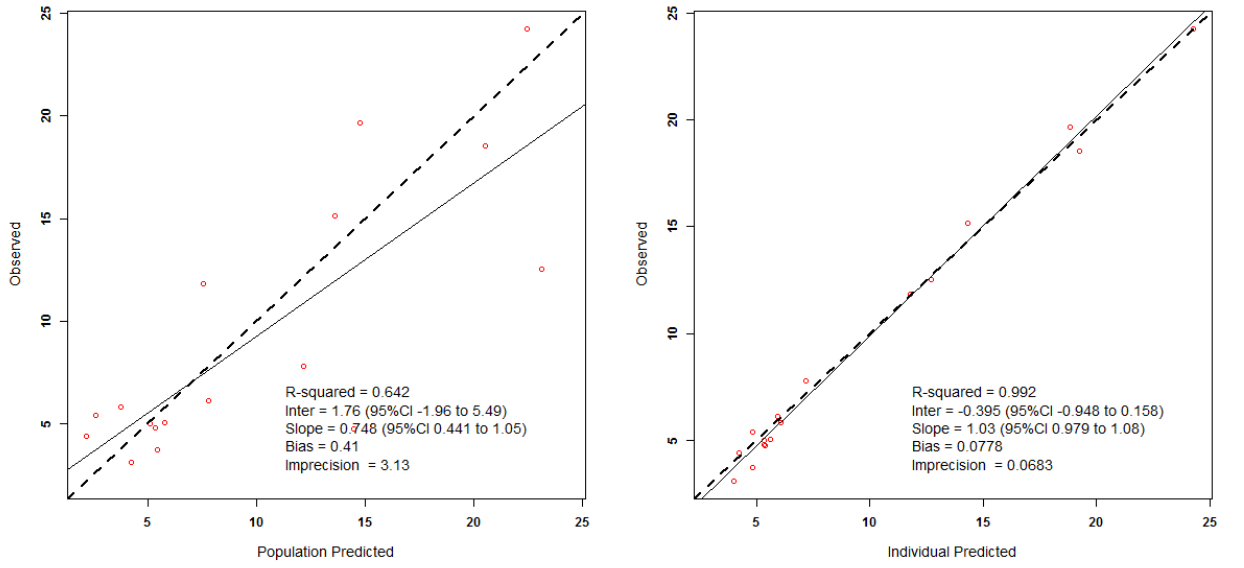

FIGURE 1 - R^2 value and bias from population (A) and individual (B) observed versus predicted plots obtained from the final model; and the weighted residual plot versus time and concentration (C).

The inclusion of the normalized covariables creatinine clearance, age, and body mass index resulted in a statistically significant improvement of log-likelihood, the goodness-of-fit plots from the former model (R^2< 0.2), as well of the R^2 value, being thus included in the final equation. The final model was represented by the following equation:

```
CL=CLni*((CLcr/218)**0.75)*((age/7)**0.75)*16.7/BMI
&IF(ICU.EQ.1) THEN CL=CLi*((age/7)**0.75)*16.7/BMI
V=Vni
&IF(ICU.EQ.1) THEN V=Vi
Ke=CL/V
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Where, CL_{ni} is the clearance for patients not admitted to the ICU; ClCr is the covariable creatinine clearance; BMI is the covariable body mass index; CL_i is the clearance for patients admitted to the ICU; V is the volume of distribution; ICU is the covariable intensive care unit; V_i is the volume of distribution for patients admitted to the ICU; V_{ni} is the volume of distribution for patients not admitted to the ICU and Ke is the elimination rate constant.

The mean (SD) population PK parameter estimates from the final equation are displayed in Table II.

The goodness-of-fit of the chosen model are displayed in Figure 1 (C).

TABLE II - PK population Parameter estimates for vancomycin

Parameter	Mean	Standard Deviation	Coefficient of variation (%)	Median
CL_i(L/h)	0.255	1.23	48.072	0.357
CL_{ni}(L/h)	1.709	0.612	35.847	1.851
V_i (L)	2.808	1.991	70.915	2.544
V_{ni} (L)	0.787	0.871	110.674	0.175

(continues on the next page...)

TABLE II - PK population Parameter estimates for vancomycin

Parameter	Mean	Standard Deviation	Coefficient of variation (%)	Median
KCP	6.797	4.313	63.451	8.332
KPC	0.362	0.168	46.477	0.446

$CL_{i=}$ clearance for patients admitted to the ICU; $CL_{ni=}$ clearance for patients not admitted to the ICU; V_{i}= volume of distribution for patients admitted to the ICU; $V_{ni=}$ volume of distribution for patients not admitted to the ICU; KCP= Central to peripheral rate constant; KPC= Peripheral to central rate constant

DISCUSSION

Although there are a few previous reports evaluating vancomycin kinetics in children (Hoang *et al.,* 2014; Moffet *et al.*, 2018; Hahn *et al.*, 2015; Krivoy *et al.*, 1998; Tkachuk, Collins, Ensom, 2018), this is a pioneering study conducted in Brazilian patients. The results show that glycopeptide pharmacokinetics is related to creatinine clearance, age, and body mass index. In addition, the proposed model has a good predictive capacity, both for individuals (r^2= 0.992) or population (r^2= 0.642) and predicts individual concentrations well, supporting its choice for Gram-positive pathogens that remain resistant, such as MRSA.

Several factors affect vancomycin pharmacokinetics, especially the covariable age. Studies on preterm newborns have shown that the pharmacokinetic parameters of vancomycin are influenced not only by gestational age, but also and more significantly, by post conceptual age and body weight. In older children, an increased vancomycin body clearance with age, with a peak around 4 years was demonstrated (Spivey, Gal, 1986; Schaad, McCracken, Nelson, 1980; Sande, Mandell, 1991), justifying a higher final clearance than the initial clearance.

n addition, the body mass index influence on vancomycin kinetics has been described in previous reports (Pan *et al.*, 2020; Leong, Boro, Winter, 2011; Vance-Bryan *et al.*, 1993; Bauer, Black, Lill, 1998). Vance-Bryan *et al.* (1993) verified that an increase of 10 Kg in total body weight would increase the volume of distribution to 8.1 L. Similarly, Pan *et al.* (2020) demonstrated a progressive decrease in serum vancomycin concentrations concomitant to an increasing BMI. These results can be explained by vancomycin hydrophilicity and increased adipose tissue, since Grace (2012) found an altered volume of distribution of vancomycin in obese patients when compared with non-obese patients associated with those factors.

Finally, a higher drug transfer rate from the central compartment to peripheral compartment than peripheral compartment to central compartment was verified, evidencing the wide vancomycin distribution in tissues, with a decreased return, despite its hydrophilicity (Hanrahan, Lipman, Roberts, 2016).

Two-compartment pharmacokinetic models for vancomycin in pediatric patients have been previously described in the literature (Seay *et al.,* 1994; Capparelli *et al.*, 2001; Marsot *et al.*, 2012; Moffett *et al.*, 2018). Similarly, Neely *et al.* (2014), describes a two-compartment model for vancomycin, parameterized with first order elimination (Ke) from the central compartment with a volume (Vc) and linear transfer to (KCP) and from (KPC) the peripheral compartment.

Nevertheless, there are a few methodological limitations in this report. First the sample size, which can compromise the model predictive capacity. Second, this study was not delineated to measure clinical outcomes, such as the development of bacterial resistance. However, this study can provide a strong positive impact on the patient's prognosis, since the knowledge of their pharmacokinetics and pharmacodynamics influence control of the infection.

CONCLUSION

In this study, we verified a relevant pharmacokinetic variability for vancomycin in pediatric patients, more significantly for the final volume of distribution, which showed the highest coefficient of variation. Further studies are required to validate our findings.

Considering the vancomycin pharmacokinetic variability and bacterial susceptibility, population pharmacokinetic modelling may contribute to optimize individual vancomycin dosing in clinical practice (Reis, Grisi, 1996; Timothy, Welty, Alan, 1994; Balch *et al.,* 2015; Marsot, 2018).

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CONFLICT OF INTEREST

The authors declare no conflict of interest with respect to the publication of this manuscript.

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