J Infect Chemother 23 (2017) 154–160

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Assessment of optimal initial dosing regimen with vancomycin pharmacokinetics model in very low birth weight neonates

Hideo Kato [a, b], Mao Hagihara [a, b, *], Naoya Nishiyama [a], Yusuke Koizumi [a], Hiroshige Mikamo [a], Katsuhiko Matsuura [a, b], Yuka Yamagishi [a]

[a] Department of Infection Control and Prevention, Aichi Medical University School of Hospital, Japan
[b] Department of Pharmacy, Aichi Medical University School of Hospital, Japan

ARTICLE INFO

Article history:
Received 26 May 2016
Received in revised form
11 November 2016
Accepted 25 November 2016
Available online 22 December 2016

Keywords:
Vancomycin
Population pharmacokinetic analysis
Pharmacokinetics
Pharmacodynamics
Very low birth weight neonates

ABSTRACT

Introduction: Pharmacokinetic of vancomycin in very low birth weight neonates showed big variety, and limited data were available due to very minor population. These facts make it difficult to adjust its optimal initial dosage. Therefore, this study was to develop optimal dosing regimen of vancomycin in very low birth weight neonates.

Methods: Between 2010 and 2015, low birth weight neonates (≤1500 g) were included in a population pharmacokinetics analysis. Based on the pharmacokinetic parameters we estimated, we simulated individual blood concentrations of vancomycin and evaluated the probability of its pharmacokinetics/pharmacodynamics (PK/PD) target attainment, such as 24-h area under the concentration–time curve (AUC_{24})/MIC (≥400) and blood trough concentration (10–20 μg/mL), as primary measure for several dosing regimens by Monte Carlo simulation method.

Results: Ten patients were prescribed vancomycin and detected its blood concentrations as routine pharmacy practice to adjust the dosage. A one-compartment model was used and clearance significantly correlated with serum creatinine and the volume of infusion. In this model, vancomycin dose at 10 mg/kg three times a day (TID) was predicted to result 86.7% of neonates for an MIC of 1 μg/mL achieving AUC/MIC of ≥400 and 30.6% of the neonates for an MIC of 2 μg/mL. Moreover, the probability of reaching the target trough concentration was 70.5% for patients treated with vancomycin 10 mg/kg TID.

Discussion: We recommended vancomycin 10 mg/kg TID as initial dosage regimens for low birth weight neonates infected with the pathogens showed MIC of ≤1 μg/mL.

1. Introduction

Vancomycin is a glycopeptide antibiotic used in the treatment of relatively resistant gram positive infections for neonates. Coagulase-negative staphylococci (CNS), most of which are methicillin-resistant, and methicillin-resistant *Staphylococcus aureus* (MRSA) are the most frequent pathogen for late-onset (72 h post-birth) septicemia, sepsis-related mortality and morbidity rates were even higher in extremely preterm neonates because of their innate immunological immaturity [1–6]. Hence, vancomycin continues to be widely prescribed in neonatal intensive care unit (NICU), and optimizing vancomycin dosing to rapidly achieve adequate antibiotic exposure is imperative in treating neonatal sepsis, particularly when treating invasive MRCNS and MRSA infections [7].

In general, the ratio of the 24-h area under the concentration–time curve (AUC) to the minimum inhibitory concentration (MIC) of ≥400 is the best predictor of successful outcomes when treating invasive MRSA infections with vancomycin [7]. To achieve an AUC/MIC of ≥400 in adults, a vancomycin trough of 15–20 μg/mL is recommended [8]. Previous study suggested targeting a trough concentration of >10 μg/mL to achieve an AUC of ≥400 in neonates [9]. Of note, AUC is not routinely utilized to assess the appropriateness of vancomycin dosing in neonates when treating invasive MRSA infections, presumably due to practical limitations associated with calculating the AUC_{24}. Additionally, recommended doses of vancomycin for neonates have not yet been established,

* Corresponding author. 1-1, Yazakokarimata, Nagakute, Aichi, 480-1195, Japan. Fax: +81 0561611842.
E-mail address: hagimao@aichi-med-u.ac.jp (M. Hagihara).

http://dx.doi.org/10.1016/j.jiac.2016.11.009
1341-321X/

because a few clinical studies have been conducted to evaluate pharmacokinetic characteristics of neonates, while traditionally, for intermittent administration, various permutations of dose and dose frequency are often faithfully applied in order to obtain target plasma concentration.

The pharmacokinetics of vancomycin is highly variable among neonates and limited data were available, especially for low birth weight neonates (≤1500 g), due to very minor population. These facts make dosing challenging in this population. These differences are largely determined by the change in the amount of body water and maturation of renal function in the first weeks of life, both in preterm newborn infants [10]. Hence, there are pharmacokinetic differences even though between infants and very low birth weight neonates [11]. However, adequate drug exposure is critical, especially when treating MRSA infections.

Therefore, the objective was to develop optimal dosing regimen of vancomycin using the pharmacokinetic data of vancomycin in very low birth weight neonates (≤1500 g) with population pharmacokinetic analysis. It also assessed the relationship between vancomycin trough concentration and AUC in very low birth weight neonates to conduct an external evaluation of this published pharmacokinetic model and to enhance our understanding of the relationship between vancomycin trough concentration and AUC_{24} in neonates.

2. Patients and methods

2.1. Patients

This work was a single-center, retrospective study. All patients admitted to NICU in Aichi Medical University Hospital between January 2010 and July 2015. The candidate in this study was the very low birth weight neonates (≤1500 g). Most neonates were infected with MRSA or MRCNS. Relevant clinical background and laboratory data were collected at appropriate intervals during the vancomycin treatment. We excluded the neonates treated with vancomycin for <2 days, body weight of >1500 g or postnatal age (PNA) of >30 days, and neonates who lacked the laboratory data necessary for the present study. The study protocol was reviewed and approved by a local institutional committee in Aichi Medical University.

2.2. Data collection

At least 3 days before vancomycin treatment started, we retrospectively collected usual clinical and demographic data such as gender, serum creatinine (Scr), estimated glomerular filtration rate (eGFR), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and blood urea nitrogen (BUN). The eGFR estimate was calculated according to the Schwartz formula [12]. Clinical characteristics at birth (eg, gestational age (GA) in weeks, birth weight in kg), as well as characteristics at the moment of therapeutic drug monitoring (TDM) (eg, PNA in days, postconceptional age (PCA) in weeks, current weight in kg, volume of infusion and urinary volume in mL/day) and serum vancomycin concentration were extracted from the patient files.

Drug concentration data were collected as part of the routine TDM data. Vancomycin was measured in the serum of all neonates at least once, and the dates and times of the dose and concentration measurements were accurately documented for all neonates. The vancomycin concentrations were determinate with an enzyme multiplied immunoassay using a vancomycin kit (Roche Diagnostics K., K., Tokyo, Japan). The limit of quantification of this assay is 1.7 μg/mL, and the coefficients of intra- and inter-assay variation are less than 5% each.

2.3. Population pharmacokinetic analysis

2.3.1. Basic model

The pharmacokinetic parameters of vancomycin were calculated with individual serum-concentration data using Phoenix NLME, a component of WinNonlin ver. 6.3 (Pharsight Corporation, Mountain View, CA).

Both one- and two-compartment models with first-order elimination were tested. We used an exponential random effects model for each pharmacokinetic parameter. We assumed the random effects to be normally distributed with a mean of 0 and a variance of ω^2. The model has two components: (i) a structural model that characterizes the concentration−time relationship and (ii) random-effect models, including inter-individual variability in the PK parameters, and residual error, including intra-individual variability and measurement errors. Assumptions about the base population pharmacokinetics model (one-versus two-compartment and residual variability) were evaluated based on the objective function value, agreement between observed and predicted vancomycin concentration, and visual inspection of the distribution of the weighted residual plots.

The model also included estimates of the residual random error for vancomycin (ε) the residual random errors included assay errors, individual changes in the pharmacokinetic parameters, and model misspecification errors. The distribution of ε was assumed to obey a normal distribution and was characterized by a mean of 0 and variance, σ2, which can be estimated by WinNonlin. The residual variability was modeled by an additive error according to the equation $Cp = F + \varepsilon$, where Cp is the observed serum vancomycin concentration and F is the concentration predicted by the compartment model.

2.3.2. Covariate model building

The influences of the following covariates at the initiation of treatment on the pharmacokinetic parameters of vancomycin were tested: seven demographic variables (GA, birth weight, PNA, PCA, current weight, volume of infusion and urinary volume), and biochemical marker (serum creatinine, eGFR).

Covariates that might influence the pharmacokinetics of vancomycin were stepwise added one by one to the basic model. For each model, the improvement in the fit obtained by the addition of a fixed-effect variable to the overall model was assessed based on the difference in the objective function, which is equal to −2 (log likelihood difference). This difference is asymptotically distributed, like χ^2 with degrees of freedom equal to the number of added/reduced parameters. A change in the objective function value (⊿OBJ) of 6.63 with a freedom of unity represents a significant ($p < 0.01$) model improvement. Similarly, we estimated the influence of a covariate on V.

2.3.3. Final model determination

We graphically studied the influence of covariates on their related pharmacokinetic parameters. Outliers were studied and excluded from the analysis when incomplete data collection was suspected. A backward selection method was used in order to obtain a final model in which all covariates had a $p < 0.01$ using the likelihood-ratio test.

2.3.4. Model evaluation

Basic goodness-of-fit plots, individual weighted residuals (IWRES), normalized prediction distribution errors (NPDE) over time and visual predictive checks were used to assess the model. Moreover, a bootstrap resampling procedure, which is often used to evaluate the stability and robustness of a population model via repeated random sampling, was conducted [13].