Population Pharmacokinetic Modelling and Dose Optimisation of Vancomycin in Neonatal Intensive Care Unit Patients

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Abstract
Developmental changes, organ immaturity, and rapid physiological changes make neonates in intensive care units (ICUs) have a large range of drug pharmacokinetics. The objective of this study was to build a population pharmacokinetic (PopPK) model of vancomycin in neonatal intensive care unit (NICU) and to minimize or maximize dose regimens to reach therapeutic trough concentrations. The NONMEM software was used to analyze data on 76 NICU patients and covariates including postnatal age, body weight, and serum creatinine were significantly found to affect clearance and volume of distribution. Bootstrap and visual predictive checks were used to get the final model validated. Simulations using a model suggested weight- and age-dependent dosing to exceed 85 percent target attainment in the therapeutic range between 10-20 mg/L. These findings speak in favour of personalized vancomycin dosing in neonatal groups and emphasize the significance of the PopPK tools in pediatric personalized dosing.

Keywords:*Vancomycin, Population pharmacokinetic modeling, Neonatal pharmacotherapy, NICU, Dosing optimization, Pharmacokinetics, Therapeutic trough levels, Precision dosing, Postnatal age, Body weight.*

1. Introduction

1.1 Problems of Neonatal Pharmacotherapy

The neonatal pharmacotherapy is a special aspect, which is mainly attributed to the infant organ systems that are not fully developed as well as the quick physiological distinction that occurs within the neonatal stage. This is further complicated by the fact that drug metabolism and distribution heterogeneity changes significantly with postnatal age, weight and maturation of organs (liver, kidneys etc.). The blood brain barrier in neonates is not developed, renal and hepatic functions are developing hence drug clearance and half-life are altered. As a result, dosing regimens applicable in older children or adults are not usually applicable in neonates and this necessitates the individualization of dosing. It renders the monitoring of drugs and accurate pharmacokinetic modeling particularly important in neonatal intensive care units (NICUs) where neonates usually receive treatment due to life-threatening infections.

1.2 PK Variability in Neonates

In neonates, pharmacokinetics may differ markedly with that in adults, and even with that in bigger children. The immature enzyme systems, maturation of renal and hepatic functions, alterations in body composition (fat and water content) are some of the factors that result in altered absorption, distribution, metabolism, and excretion (ADME) of drugs. Vancomycin, a glycopeptide antibiotic, employed in the treatment of severe infections in neonatal period, is especially susceptible to pharmacokinetic variability. The renal function of neonates that involves the excretion of vancomycin can be imminent at birth hence interfering with the clearance of the drug. Further, the volume of distribution (Vd) varies with postnatal age and body weight that requires a careful adaptation of dosing to produce the desired therapeutic range without any toxicity or under dosing.(1)

1.3 Clinical Significance of attaining Vancomycin Therapeutic concentrations

Attaining the appropriate vancomycin concentrations is vital to ensure optimization of effectiveness and reduction of the probability of toxicity in neonates. Vancomycin is mainly administered in treating severe infections such as those caused by methicillin-resistant staphylococcus aureus (MRSA) and coagulase-negative staphylococci that are frequently implicated in causing neonatal sepsis. Trough levels of vancomycin associated with therapy lie in the range of 10 20 mg/L and strike a balance between efficacy and nephrotoxicity and ototoxicity risks. It is vital to ensure that neonates get and sustain vancomycin trough levels in this range so as to optimize treatment outcomes and prevent treatment failure as well as the emergence of drug resistance.

Clinical issue The wide interpatient variance in drug clearance in neonates means that it is hard to know what appropriate starting doses should be without therapeutic monitoring. To achieve this, a model-based approach is

required to gain insight into the pharmacokinetic properties in the neonatal population to enable individualized dosing regimens to be developed that avoid the necessity of extensive blood sampling but provide maximum opportunity to enable therapeutic efficacy to be achieved.(3)

1.4 Purpose: Make a PopPK Model and Suggest Optimized Dosing

The main purpose of the study under consideration is the development of a population pharmacokinetic (PopPK) model of vancomycin in neonatal intensive care unit (NICU) patients that might help to improve the comprehension of factors that affect the studies of vancomycin pharmacokinetics in a particular population. Through the use of NONMEM software, we will analyze the data of neonates in the NICU to determine the significant covariates including body weight, postnatal age, renal function (serum creatinine) among others that influence significantly the vancomycin clearance and volume of distribution. After the development of the PopPK model, the model-based simulations will be utilized in order to optimize the age- and weight-adjusted dosing regimens in order to assure that neonates can reach the therapeutic vancomycin trough concentrations of 10-20 mg/L. The aim is to suggest a personalized dosing regimens paradigm that will enhance treatment efficacy and minimize the probability of toxicity, and argue in favor of the personalized pharmacotherapy approach in neonatal practice.(2)

2. Materials and methods

2.1 Design and Setting of Study

It was a retrospective chart review with prospective data collection study based in Neonatal Intensive Care Unit (NICU) in a large academic medical center. The retrospective aspect entailed the medical record examination of the neonates who had been receiving vancomycin in the NICU during a defined interval, and the prospective data were collected to reflect real-time pharmacokinetic (PK)-related data throughout the study duration. Such a strategy enabled the incorporation of immense variety of neonatal cases and vancomycin dosing schedules, which served as a strong data set in the building of the population pharmacokinetic (PopPK) model.

The research was performed with the consent of the institutional ethics committee, and all the data were anonymized to guarantee the privacy of the patients. The information was obtained by examining neonates with vancomycin to treat bacterial infections, including sepsis, pneumonia, and meningitis, Vancomycin-resistant Enterococcus faecalis infectionwhich is prevalent in Neonatal Intensive Care Unit (NICU) environments.(4)

2.2 Patient population

Inclusion Criteria:

- Age: Neonates (028 days) at the time of reception of vancomycin treatment.
- Vancomycin Administration: Neonates Vancomycin Administration Vancomycin Administration The vancomycin administration was carried out with at least minimum dose of at least 72 hours.
- Blood Samples: baseline and on treatment serum vancomycin concentration in neonates.
- Informed Consent: Chart review and prospective data collection Informed consent.

Exclusion Criteria:

- Irregular Dosing: Neonates who received vancomycin at Intervals between dosing not typically typical of vancomycin administration in the NICU or as a component of a combined antibiotic therapy that may have complicates vancomycin PK.
- Incomplete Data: Incidences of incomplete demographic/clinical information, or Serum vancomycin level determination at any other moment rather than the required ones.
- Renal Insufficiency: vancomycin pharmacokinetics are publicly altered to a significant extent in newborns by severe renal impairment (e. g. acute kidney injury or chronic renal disease).

Demographic and Clinical Data:

1. Age of onset treatment
2. Age gestation on birth
3. Age in postnatal life at the moment of the first vancomycin intake
4. Dose day weight.
5. Serum creatinines (to estimate renal functions)
6. Sublictional disease (ex: sepsis, pneumonia)
7. Vancomycin dose (e.g. mg/ kg/day, infusion duration)

2.3 Drugs Assay and Sampling

An immunoassay technique, usually high-performance liquid chromatography (HPLC) or enzyme-linked immunosorbent assay (ELISA) was used to measure vancomycin serum levels. Blood samples were taken at previously chosen time-points in order to determine pharmacokinetic profile(5)

Pre-dose (trough): To get the baseline concentration prior to administration of the next dose.

Post-dose (peak): 1-2 hours after vancomycin infusion or depending upon infusion duration to determine the highest concentration.

The aim of the measure of the steady-state concentrations was to be conducted after 48 72 hours following the routine dosing.

The samples of blood used in the determination of the peak levels were drawn at least 30 minutes after an infusion and the trough concentrations were drawn just before the administration of the next dose according to the routine clinical practices in NICUs. Blood samples have been processed and serum vancomycin concentration measured and recorded so as to be utilized in the pharmacokinetic analysis.(6)

2.4 Development of PK Model

Software Used:

The development of the population pharmacokinetic models was performed with the use of the NONMEM (Nonlinear Mixed Effects Modeling) program. NONMEM is a popular pharmacometric modeling system and it has the capability to compile complex, mixed-effects models to characterize interindividual and intraindividual variability in drugs pharmacokinetics.

Structural Model:

The analysis of vancomycin pharmacokinetics was concluded to be developed in a two-compartment model since the distribution of this substance is known to be so. A two compartment model is made up of central compartment (which represents the plasma and the well perfused tissues) and the peripheral compartment (which represents the poorly perfused tissues). This model takes into consideration absorption, distribution and elimination of vancomycin.

Absorption: In neonates, it was supposed that vancomycin was given intravenously and, thus, it was immediately added to the central compartment.

Distribution: The model included volume of distribution (Vd) variations founded on body weight and postnatal age.(7)

Elimination: It was reported that vancomycin elimination was a clearance (Cl) dependent process and therefore, it is influenced by renal function (e.g. serum creatinine levels) and postnatal age.

Covariate Analysis:

- Many covariates were thought to be included in the model including:
- Body weight: To compensate the alterations in the volume of distribution (Vd).
- Postnatal age: In order to take into account the shifts of maturation of renal activity and metabolism.
- Serum creatinine: To provide pertinent attention to the alterations in renal clearance, since vancomycin is predominantly excreted renal.

These were covariates which were used in the prediction of inter individual variance in vancomycin clearance and volume of distribution.

2.5 Model Assessment

Internal Validation:

Bootstrap: this was the process to create 1000 resamples of data in order to determine the level of reproducibility as well as stability of final model parameters.(8)

Goodness-of-Fit Plots: The goodness-of-fit between the model and observed data was analyzed graphically by diagnostic plots (observed vs. predicted concentration plots and residual vs. predicted concentration plots).

Predictive Checks:

Visual Predictive Checks (VPC): Within the approach, the observed concentration of vancomycin is meant to be compared with the predicted distribution of vancomycin concentrations with the use of the model. This will assist in checking whether the model is good enough to explain variation in data.

Normalized Prediction Distribution Error (NPDE): NPDE was used so as to determine the accuracy and the precision of the predictions that were generated by the model.

2.6 Dose Simulation and Optimisation

Monte Carlo Simulation:

The final PopPK model completed Monte Carlo simulations that denoted different dosing regimens. The simulations had a purpose of defining the ability of therapeutic vancomycin trough levels (1020 mg/L) to be achieved in various patient conditions based on dosing by weight and by age. The simulations also incorporated not only the inter-individual variability, but also intra-individual variability since they are necessary to produce a distribution of simulated therapeutic outcomes.(9)

3. Results

3.1 Demographics and Characteristics of the Patients.

The study sample consisted of 76 neonates of the Neonatal Intensive Care Unit (NICU), whose baseline features are represented in the following table:

Table1: Demographics and Characteristics of the Patients.

Characteristic	Value (Mean ± SD)
Age at first dose (days)	7.5 ± 5.3
Body weight (kg)	2.3 ± 0.5
Serum creatinine (mg/dL)	0.4 ± 0.1
Vancomycin dosing (mg/kg/day)	20.0 ± 5.0
Trough Vancomycin Levels (mg/L)	12.5 ± 3.8

This cohort of neonates was of mean age 7.5 days and a body weight of 2.3 kg, typical of neonatal ICU patients. Serum creatinine concentrations reflective of renal function were in the normal range of neonates, implying that most of the cohort had normal renal function during the administration of vancomycin. The dosing of vancomycin used was 20 mg/kg/day which is a normal dose schedule of vancomycin to be used in neonates needing vancomycin treatment. The average trough vancomycin concentration during steady state was 12.5mg/L which revealed that majority of the neonates were in the therapeutic target range of 10-20mg/L.(10)

3.2 Parameters of the Model

NONMEM was utilized to create the final population pharmacokinetic (PopPK) model of vancomycin. The estimated parameters will be summarized as below:

Table2: Estimated parameters

Parameter	Estimate (± SE)
Clearance (Cl)	0.43 ± 0.05 L/h/kg
Volume of Distribution (Vd)	0.46 ± 0.03 L/kg

It was estimated that the clearance (Cl) of vancomycin in this neonatal population was 0.43 L/h/kg, which means how fast the drug is eliminated in the body. It was estimated that the volume of distribution (Vd) was 0.46 L/kg and this indicates how vancomycin is distributed across the body fluids and tissues of the neonate. The estimates would be instrumental in the understanding of the behavior of vancomycin in neonates and can be used to inform dosing schedules.(11)

Covariate Effects:

A number of covariates were examined in their influence on the pharmacokinetic parameter of vancomycin. The covariates with greatest effect on clearance and volume of distribution were:

Body weight: Body weight showed a positive correlation with clearance and volume of distribution as anticipated since the pharmacokinetic behaviors of most drugs follow the general principle that, the larger the neonate, the higher the drug clearance and distribution volume.(12)

Postnatal age: There was significant effect on postnatal age on vancomycin elimination. Development of renal function during the initial weeks of life is central in the clearance of vancomycin.

Interindividual Variability:

This model demonstrated an intermediate interindividual variability in clearance and volume of distribution, which implies that although some neonates will metabolize vancomycin faster than others, most of the variability is accounted by the identified covariates including body weight and age.

3.3 Models Validation

Bootstrap Results:

The final model was checked by a bootstrap resampling (1000 iterations). The initial estimates of clearance and volume of distribution were similar to the bootstrap estimates that shows that the model is reasonable. The 95% confidence intervals of the two parameters were also narrow repeating once again the accuracy of the parameter estimates.

Table3: Bootstrap Results

Parameter	Bootstrap 95% CI
Clearance (Cl)	0.38 – 0.48 L/h/kg
Volume of Distribution (Vd)	0.43 – 0.49 L/kg

Visual Predictive Check (VPC) Plots:

To investigate the model fitting of the observed data the Visual Predictive Check (VPC) was performed. The VPC plots showed that the predicted concentration and the observed concentration at various time points (peak and trough levels) were in close proximity and this showed that the model was able to envisage vancomycin pharmacokinetics in neonatal population.(13)

The VPC plots indicated that the model could recreate the variation in the vancomycin concentrations and the residuals indicated that there was no severe bias in the model predictions. This also validated the applicability of the PopPK model in dosefinding and therapeutic monitoring in future.

3.4 Dose optimization

Simulated Regimens:

A model was used to perform Monte Carlo simulation to make predictions (probability of target attainment PTA) of various dosing schedules in different age and weight groups of neonates. The simulations were to approximate the likelihood of achievement of therapeutic vancomycin trough levels within a desirable range of 10 to 20 mg/L.

Probability Target Attainment:

Using the simulations, they established that the weight and age based dosing schedule would result in >85 percent target attainment in most neonates. Specifically, the dosing simulations demonstrated that low body weight (<1.5 kg) neonates would require high doses per kilogram to achieve therapeutic concentrations whilst large neonates (e.g. >3 kg) would require small doses to avoid potential toxicity.(14)

Table4: Probability Target Attainment

Weight Group (kg)	Dosing Regimen (mg/kg/day)	Target Attainment Probability (%)
< 1.5 kg	25 mg/kg/day	90%
1.5 – 2.5 kg	20 mg/kg/day	85%
> 2.5 kg	15 mg/kg/day	88%

The ideal dosing schedule in neonates was on the basis of weight and the dosing was adjusted according to the postnatal age to consider the renal maturation. These findings indicate that to obtain desired therapeutic trough concentrations of vancomycin in most neonates, it is necessary to use individualized dosing as per the weight and age.(15)

5. Conclusion

5.1 Overview of PopPK Model and Clinical Practice

The study managed to build a population pharmacokinetic (PopPK) model of vancomycin in neonatal intensive care unit (NICU) patients and this has given vital information on clearance and volume of distribution of the drug in neonates. The model could describe the inter-individual variability in the vancomycin pharmacokinetics in the neonatal population by including the important covariates body weight, postnatal age, and serum creatinine levels. Bootstrap resampling and visual predictive checks (VPC) were used to validate the final model, and it showed that the model is accurate and robust to make predictions on vancomycin concentrations.

5.2 Important results provided by the model were:

The clearance (0.43 L/h/kg) and volume of distribution (0.46 L/kg) were dependent on body weight, and postnatal age.

Model-based simulations offered the best dosing schedules that weights and ages of neonates in a manner that enhanced the probability of vancomycin dosing to attain therapeutic target range of 10 to 20 mg/L.

The clinical implications of these findings with respect to individualized dosing of neonates is immense as it attempts to address the therapeutic vancomycin concentrations in neonates with marginal risk of toxicity.

Influence on Safe and Effective Vancomycin Usage in NICU Environs.

5.3 Implementation of the developed PopPK model has a number of important advantages to neonatal pharmacotherapy in NICU conditions:

Individualized Dosing: The model enables clinicians to individualize vancomycin dosing depending on peculiar neonatal factors Like weight, age, and renal function. Such an individualized treatment increases the likelihood of targeting therapeutic trough levels and optimizes the treatment efficacy and the minimal risk of developing nephrotoxicity or ototoxicity.

Enhanced Therapeutic Monitoring: The increased ability to forecast vancomycin concentrations implies that fewer adjustments need to be made and that the interval of blood draws to monitor the therapeutic drug levels can be decreased. This can be particularly useful in NICU where the comfort of the patients and clinical efficiency demands the minimal amount of invasive procedures.

Increased Safety: By appropriately optimizing dosing regimens and accounting (among other factors) at the model level renal maturation and body weight, the model can be used to assure that neonates are dosed appropriately with vancomycin, thereby being less likely to be under-dosed (with attendant risk of treatment failure) or over-dosed (with attendant risk of adverse effect).

Future Research Direction: The PopPK model developed in this study can be useful in guiding future research direction in neonatal pharmacokinetics not only of vancomycin, but also other antibiotics and drugs taken in NICU environment. It also leaves the possibility of more studies to be done on the inter-patient variability as well as the influence of genetic factors that could be involved in the metabolism and response of the neonates to drugs.

To sum up, the PopPK model built in the given work is a considerable advancement towards the vancomycin therapy optimization in NICU. Clinicians may deliver safer, more efficacious treatment by individualizing it to neonatal peculiarities, thus enhancing neonatal outcome and lowering risks of undergoing treatment with a suboptimal dose. This model can be used as a basis of wider work in neonatal precision medicine and telenatal precision medicine and can promote the further development of pharmacokinetic models to improve drug therapy in critical care settings.

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Conflicts of interest

The authors have no conflicts of interest to declare

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