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Stéphanie Leroux[1,2,3], Evelyne Jacqz-Aigrain[1,2,4], Valérie Biran[5], Emmanuel Lopez[6], Doriane Madeleneau[7], Camille Wallon[6], Elodie Zana-Taïeb[7], Anne-Laure Virlouvet[5], Stéphane Rioualen[5], Wei Zhao [8,9#]on behalf of VANCO IVC study group*

*The full list of VANCO IVC study group can be found at the end of the article

1. Department of Paediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, APHP, Paris, France
2. EA7323, Université Paris Diderot-Université Paris Descartes, Paris, France
3. Department of Neonatology, CHU de Rennes, Rennes, France
4. Clinical Investigation Center CIC1426, INSERM, Paris, France
5. Neonatal Intensive Care Unit, Hôpital Robert Debré, APHP, Paris, France
6. Neonatal and Pediatric Intensive Care Unit, Hôpital Clocheville, Tours, France
7. Neonatal Intensive Care Unit, Hôpital Cochin Port-Royal, APHP, Paris, France
8. Department of Pharmacy, Qian-Fo-Shan Hospital Affiliated to Shandong University, Shandong University, Jian, China
9. Sino-French Pediatric Research Center, Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Shandong University, Jinan, China

Correspondence:

Prof Dr Wei Zhao

Department of Pharmacy, Qian-Fo-Shan Hospital Affiliated to Shandong University, Shandong University, 250014, Jian, China

E-mail: wei.zhao@rdb.aphp.fr

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Abstract

Background and objective: Pharmacokinetic modeling was often applied to evaluate vancomycin pharmacokinetics in neonates. However, clinical application of the model-based personalized vancomycin therapy is still limited. The objective of the present study is to evaluate the clinical utility and safety of a model-based patient-tailored dose of vancomycin in neonates.

Methods: A model-based vancomycin dosing calculator, developed from a population pharmacokinetic study, has been integrated into the routine clinical care in 3 NICUs (Robert Debré, Cochin Port Royal, Clocheville Hospitals) between 2012 and 2014. The target attainment rate, defined as the percentage of patients with a first therapeutic drug monitoring vancomycin serum concentration achieving the target window of 15-25 mg/L, was selected as endpoint for evaluating the clinical utility. The safety evaluation was focused on nephrotoxicity.

Results: The clinical application of the model-based patient-tailored dose of vancomycin has been demonstrated in 190 neonates. Mean (SD) gestational and postnatal ages of the study population were 31.1 (4.9) weeks and 16.7 (21.7) days, respectively. The target attainment rate increased from 41% to 72% without any case of vancomycin-related nephrotoxicity.

Conclusion: This proof-of-concept study provides evidence for integrating model-based antimicrobial therapy in neonatal routine care.

Introduction

Neonatal bacterial sepsis, exacerbated by neonatal immunodeficiency (1), remains a major cause of mortality and morbidity in newborns (2). Vancomycin is widely used for the treatment of late onset sepsis caused by methicillin resistant *staphylococcus aureus* and coagulase-negative *staphylococci* in neonatal intensive care units (NICUs) (3), however the clinical use of vancomycin is still hampered by its narrow therapeutic index and high pharmacokinetic variability (4). Indeed, de Hoog et al. reported that vancomycin clearance and half-life varied between 0.63 and 1.4 mL/kg/min, and between 3.5 and 10 hours in neonates, respectively (4). The common adverse effects of vancomycin are nephrotoxicity and ototoxicity, however it has shown that neonates were better tolerated with vancomycin compared with adults. The safety data of high dosing regimen and long-term follow-up are still lacking."

Pharmacokinetic modeling approach is often applied to evaluate and optimize antimicrobial therapy in neonates (5). To date, vancomycin is one of the most studied antimicrobials and numerous studies have been published to characterize its pharmacokinetic parameters and to identify individual factors influencing variability (6). However, the clinical application of the model-based personalized vancomycin therapy is still limited. The objective of the present study was to evaluate the clinical utility and safety of the patient-tailored dose of vancomycin in neonates.

Methods

Neonates receiving vancomycin as a continuous infusion in one of three NICUs (Cochin Port Royal, Robert Debré and Clocheville Hospitals) were enrolled between June 2012 and November 2014. This study was designed in accordance with legal requirements and the Declaration of Helsinki, registered at the Commission Nationale

Informatique et Liberté (CNIL), and approved by the local research ethics committee (Comité d' Evaluation de l'Ethique des Projets de Recherche Biomédicale [CEERB]).

Model-based patient-tailored dose of vancomycin

A special training was organised in each NICU: we firstly informed the clinical pharmacology of vancomycin, its pharmacokinetic variability and a large variation of dosage schedules currently used. We then explained the principles of individual dosage adaptation and how we developed the excel dosing calculator using the results from our published population pharmacokinetic model (6):

In order to calculate the patient-tailored dosing of vancomycin for each neonate, neonatologists had to enter four patient's covariates in the calculator, including birth weight (g), current weight (g), postnatal age (PNA, day) and serum creatinine concentration (µmol/L) measured within 48 hours of starting vancomycin treatment. The developed calculator was locked and no other information was required. Patient-tailored dose is calculated automatically by using the following pharmacokinetic equations:

Loading dose (mg) = Target concentration (mg/L) x V (L)

Maintenance dose (mg/24 h) = Target concentration (mg/L) x CL (L/h) x 24h

where V (L) and CL (L/h) are calculated based on our model [7]::

$V = 0.791 \times (\text{current weight}/1416)^{0.898}$

$CL = 0.0571 \times (\text{current weight}/1416)^{0.513} \times (\text{birth weight}/1010)^{0.599} \times (1 + 0.282 \times (PNA/17)) \times (1/(\text{serum creatinine}/42)^{0.525})$

where current weight and birth weight are in g, PNA in days, serum creatinine in µmol/L and target concentration in mg/L.

The loading dose is infused over 60 minutes and followed by the maintenance dose administered as continuous infusion over 24 hours. Only patients with complete information were included into the final analysis.

Clinical utility and safety

The target attainment rate was selected as the endpoint for evaluating the clinical utility of the patient-tailored dose. It was defined as the percentage of patients with a vancomycin serum concentration within the target window of 15-25 mg/L, calculated using the first therapeutic drug monitoring (TDM) sample taken 6-24 hours after starting vancomycin treatment. This TDM practice has became a part of the routine clinical care in the 3 NICUs. One TDM sample per patient (0.5 mL) was required. The relative error to the concentration of 20 mg/L [calculated using the equation: (observed concentration (mg/L) – 20) / 20] was also used to evaluate the impact of covariates on the performance of patient tailored-dose.

The safety evaluation was focused on nephrotoxicity, which was evaluated based on changes in serum creatinine concentrations from baseline obtained within 48hours of starting vancomycin administration. Nephrotoxicity was defined as either a two-fold increase or increase by at least 0.6 mg/dL from the start and any time until the end of vancomycin therapy (7). The causality of nephrotoxicity was analyzed individually to discuss potential relation with vancomycin.

Analytical method of vancomycin

The serum vancomycin trough concentrations were determined by fluorescence polarisation immunoassay using a Cobas Integra system (Roche Diagnostics, Meylan, France). The lower limit of quantification and coefficients of variation were 0.74 mg/L and <3.3% respectively. The TDM samples were analyzed locally in the pharmacology lab of each hospital according to clinical practice. All these three laboratories used the

same analytical method, and followed the same external quality control programme and good clinical practice.

Statistical analysis

Results are presented as mean, standard deviation and range. The simple linear regression was used to evaluate the potential impact of patient characteristics (birth weight, current weight, postnatal age and baseline serum concentration) on the relative error to target concentration. The permutational two-sample t-test was used to compare the characteristics of patients who had vancomycin concentration within versus out of the targeted range. Statistical analyses were conducted using R software (V.3.0). A value of $p<0.05$ was considered statistically significant.

Results

Study population

The pharmacokinetic and safety data from 190 neonates were available. The mean (SD) current weight and postnatal age were 1755.0 (872.5) grams (range, 540-4750) and 16.7 (21.7) days (range 0-196) days, respectively. Summary of the population characteristics are presented in Table 1.

Eight patients were excluded because of incomplete information (creatinine concentration was not measured). Patients were treated for suspected or proven late onset sepsis mainly caused by coagulase-negative staphylococci. Duration of treatment was 7 to 10 days for proven infections and 2 to 5 days for suspected infections.

Clinical utility of patient-tailored dose

The mean loading dose and maintenance dose were 11.1 mg/kg and 28.3 mg/kg/day, respectively. After receiving these patient-tailored doses, the mean of the first vancomycin TDM concentrations was 20.0 mg/L (10^{th}-90^{th} percentiles: 13.1-27.6). The target attainment rate was 72% (n=136) within the range of 15-25 mg/L (91% within the range of 10-30 mg/L). Only 6 patients (3.1%) had concentrations < 10 mg/L and 12 (6.3%) had concentrations > 30 mg/L. TDM results are illustrated in Figure 1.

The relative error between observed and target TDM concentrations was not significantly linked to birth weight (p=0.35), current weight (p=0.26), postnatal age (p=0.54) and baseline serum creatinine concentration (p=0.90). Moreover, no significant differences were found between patients who had vancomycin concentration within versus out of the target range, in terms of birth weight (p=0.67), current weight (p=0.65), postnatal age (p=0.69) and serum creatinine concentration (p=0.80).

Safety of patient-tailored dose

Among the 190 neonates receiving the patient-tailored dose of vancomycin, only 2 (1.1 %) patients developed nephrotoxicity. The two neonates were 22 days old (birth weight 760g) and 10 days old (birth weight 990g), respectively. Both of them were treated on the basis of proven coagulase negative staphylococcus infections and the increases of serum creatinine levels (the first one from 0.35 to 1.62 mg/dl, the other one from 0.52 to 1.22 mg/dl) were concomitant with the onset of hemodynamic instability requiring vasoactive drugs (noradrenaline, dopamine). The altered renal function was resolved after restitution of the hemodynamic state, without any cessation of vancomycin therapy or reduction of dose. Therefore, the rise in serum creatinine level was not considered related to vancomycin for these patients.

Discussion

The present work provides the evidence-based data to demonstrate the clinical utility and renal safety of a model-based patient-tailored dose of vancomycin in neonates. The findings from population pharmacokinetic study were successfully integrated into neonatal clinical practice to individualise vancomycin therapy, showing that the percentage of patients achieving the target concentrations rose from 41% (using the standard dosing regimen) in our previous study (6) to 72% in the present study. The patient characteristics are similar between the two studies (mean postmenstrual age of 33.8 weeks and weight of 1700 grams in our previous study). Most of the patients were preterm neonates and had low birth weight.

Due to the wide inter-individual pharmacokinetic variability of many drugs evidenced in neonates (8), dosage individualization is a key issue faced by neonatologists and pediatric pharmacologists to optimize neonatal drug treatment (9). Traditionally, the antimicrobial pharmacokinetic study in neonates was focused on average drug exposure to achieve adult levels and the neonatal recommended dose is usually administered on a mg/kg basis (10). This approach obviously simplifies the analysis of developmental changes in drug disposition and clinical conditions on pharmacokinetic parameters. It assumes an "average newborn" with an "average weight" and therefore a simple linear maturation relationship between weight and drug clearance. This simplification of the complex developmental pharmacokinetics resulted in only 41% of patients achieving the vancomycin target concentrations of 15 to 25 mg/L using the standard mg/kg based vancomycin dose (6).

According to regulatory guidelines, antibacterial agents are a good example of drugs for which the exposure-response relationship can be assumed to be similar in adults and neonates. An $AUC_{0\text{-}24}$/MIC ratio (area under the concentration-time curve over

24h at steady-state divided by the minimum inhibitory concentration) over 400h has been shown to best predict the clinical and bacteriological response for invasive methicillin-resistant *Staphylococcus aureus* infections in adults (11). Therefore, the target AUC_{0-24} of 400 mg*h/L (assumed a standard MIC of 1 mg/L) was often used as a surrogate of efficacy to optimize dose in neonates. A positive correlation between vancomycin trough concentration and risk of nephrotoxicity was demonstrated in adults (12). Vancomycin (continuous infusion) target concentration of 15 to 25 mg/L allowed achieving this target AUC and demonstrated a good safety profile in the present study.

Appropriate neonatal dosage regimen needs to integrate the rapid developmental changes during the neonatal period, as reflected by covariates influencing drug disposition (13). As vancomycin is almost entirely eliminated by the kidneys, covariates reflecting both renal maturation and renal function should be taken into account to personalize vancomycin dosage. Pharmacokinetic modeling approach has been used for many years to evaluate pharmacokinetics of vancomycin (14,15) and identify the major covariates in neonates, including weight, age and creatinine concentration. The next step is now to implement such mathematic tool into clinical practice. Using our developed population pharmacokinetic model, the patient-tailored dose regimen was established and tested prospectively using the identified covariates. In the present study, we have shown a great improvement in the target attainment rate using the patient-tailored dose. The clinical benefits of such personalized therapy are clear: the target attainment rate is reached early and will increase efficacy while reducing the risks of bacterial resistance and toxicity. In addition, the earlier target achievement will reduce the numbers of TDM samples and dosage adjustments. Obviously, the reduced blood loss in newborns has a considerable clinical benefit. Of

note, there is still a considerable number of neonates (28%) had first TDM concentration out of target range, making TDM still recommended for vancomycin therapy in neonates.

Only 2/190 (1.1%) neonates showed nephrotoxicity as quantified by serum creatinine concentration during vancomycin treatment and this was most probably related to patients' clinical condition and hemodynamic instability. In a previous study, Bhatt-Metha et al. reported 8.7% (n=6/69) newborn infants with nephrotoxicity (using the same definition that in our study) while receiving standard vancomycin dose administered as an intermittent infusion (7). Although it is not possible to directly compare these safety results because of different method of administration, our study did not evidence any deleterious effect on renal function with the patient-tailored dose of vancomycin administrated as a continuous infusion.

A limitation of our study is that all the patients were followed until the end of hospitalization and the long-term follow-up data was not available. Obviously, the developmental toxicity, e.g. ototoxicity, cannot be evaluated in our study and a long-term safety study of vancomycin is required in neonates (16). Despite the limitation of the use of creatinine concentration as a surrogate of nephrotoxicity in neonates, it allows us to compare the incidences of nephrotoxicity with previously published studies (4, 7). Numerous novel biomarkers of nephrotoxicity (i.e. Nacetyl-glucosaminidase, neutrophil gelatinase-associated lipocalin, cystatin C etc.) are being studied, however, the clinical value of these biomarkers needs to be validated in neonates (17). The training of the correct use of dosing calculator is extremely important. The impact of entering imprecise covariates information into the calculator may introduce medication error. As highlighted by the excluded patients, the serum creatinine concentration changes rapidly at the beginning of the life. The individual

dose, calculated using creatinine measured far always from day of starting treatment, may have 2-fold difference. Obviously, the error of dose calculation will increase the risks of toxicity or treatment failure.

In summary, a model-based patient-tailored dose of vancomycin administered as a continuous infusion has been successfully implemented in routine care in 3 NICUs and demonstrated positive results in terms of pharmacokinetics and safety. This study really provides a proof-of-concept for the clinical utility and safety of model-based patient-tailored dosing regimen of vancomycin in neonates. The next step will be to confirm our results with a prospective controlled trial. This innovative personalized dosing approach, certainly applicable to other antimicrobial therapy, is a promising way to optimize drug therapy in neonates.

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Conflict of Interest

The authors declare no conflict of interest related to this work.

VANCO IVC (Continuous intravenous administration of vancomycin) **study group**

Hôpital Robert Debré: Dr Stéphanie Leroux, Pr ValérieBiran, Pr Olivier Baud, Pr Evelyne Jacqz-Aigrain, Pr Wei Zhao, Dr Daolun Zhang, Dr Elsa Maksoud, Dr Thomas Storme

Hôpital Clocheville: Dr Emmanuel Lopez, Dr Camille Wallon, Pr Elie Saliba, Dr Antoine Bouissou, Dr Nadine Fakhri, Dr Armelle Bridier, Dr Camille Dubois

Hôpital Cochin-Port Royal: Dr Doriane Madeleneau, Dr Elodie Zana-Taïeb, Pr Pierre-Henri Jarreau, Dr Juliana Patkaï, Dr Marie-Stéphanie Aubelle, Dr Mayass El Ayoubi, Dr Maher Ben Laïba, Dr Clémence Lopez, Dr Charlotte Pierron, Dr Marianne Reveret, Dr Amélie Maillard, Dr Jean-Françoise Boccara, Dr Souad Kout, Dr Marie-Lucie Brunet, Dr Camille Imbert.

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Table and Figure

Table 1- Baseline characteristics of the 190 neonates

Figure 1- Vancomycin first TDM concentrations after receiving the model-based patient-tailored dose regimen in 190 neonates

Figure Legend:

The first Therapeutic Drug Monitoring samples are taken 6 to 24 hours after starting vancomycin treatment (one sample per patient)

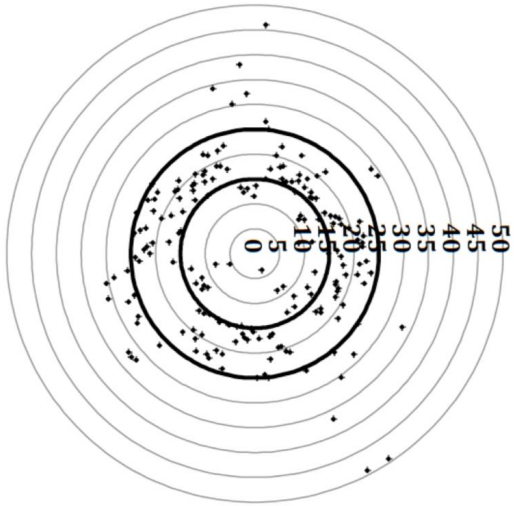
The bold lines represent the boundaries of the target concentrations

The points represent observed concentrations (mg/L)

Table 1- Baseline characteristics of the 190 neonates

	Number	Mean (sd)	Median (range)
Patients	190		
Gestational age (weeks)		31.1 (4.9)	30 (24-42)
Birth weight (g)		1563.0 (844.0)	1290 (512-4180)
Current weight (at time of dosing) (g)		1755.0 (872.5)	1525 (540-4750)
Postnatal age (days)		16.7 (21.7)	10 (0-196)
Baseline serum creatinine concentration* (µmol/L)		48.6 (21.8)	46 (14.0-125.0)
Vancomycin loading dose (mg/kg/day)		11.1 (0.6)	11.1 (9.9-12.6)
Vancomycin maintenance dose (mg/kg/day)		28.3 (9.9)	25.4 (13.0-61.0)

*within 48 hours before inclusion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