Population pharmacokinetic meta-analysis of individual data to design the first randomized efficacy trial of vancomycin in neonates and young infants

Evelyne Jacqz-Aigrain¹⁻³, Stéphanie Leroux^{1,2,4}, Alison H. Thomson^{5,6}, Karel Allegaert^{7,8}, Edmund V. Capparelli⁹, Valérie Biran¹⁰, Nicolas Simon¹¹⁻¹³, Bernd Meibohm¹⁴, Yoke-Lin Lo^{15,16}, Remedios Marques¹⁷, José-Esteban Peris¹⁸, Irja Lutsar¹⁹, Jumpei Saito²⁰, Hidefumi Nakamura²¹, Johannes N. van den Anker^{6,22-24}, Mike Sharland²⁵ and Wei Zhao^{1,26,27*}

¹Department of Pediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, APHP, Paris, France; ²Clinical Investigation Center CIC1426, Hôpital Robert Debré, Paris, France; ³University Paris Diderot, Sorbonne Paris Cité, Paris, France; ⁴Division of Neonatology, Department of Child and Adolescent Medicine, CHU de Rennes, Rennes, France; ⁵Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK; ⁶Pharmacy Department, Glasgow Royal Infirmary, Glasgow, UK; ⁷Department of Development and Regeneration, KU Leuven, Leuven, Belgium; ⁸Intensive Care, Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands; ⁹Pediatric Pharmacology and Drug Discovery, University of California, San Diego, CA, USA; ¹⁰Neonatal Intensive Care Unit, Hôpital Robert Debré, Paris, France; ¹¹Department of Pharmacology, Hôpital de la Timone, APHM, Université de la Méditerranée, Marseille, France; ¹²Service de Pharmacologie Clinique, Hôpital Sainte Marguerite, CAP-TV, 13274 Marseille, France; ¹³Aix Marseille University, INSERM, IRD, SESSTIM, Marseille, France; ¹⁴Department of Pharmaceutical Sciences, University of Tennessee Health Science Center, Memphis, TN, USA; ¹⁵Department of Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; ¹⁶School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia; ¹⁷Department of Pharmacy Services, La Fe Hospital, Valencia, Spain; ¹⁸Department of Pharmacy and Pharmaceutical Technology, University of Valencia, Valencia, Spain; ¹⁹Institute of Medical Microbiology, University of Tartu, Tartu, Estonia; ²⁰Department of Pharmacy, National Children's Hospital National Center for Child Health and Development, Tokyo, Japan; ²¹Department of Development Strategy, Center for Clinical Research and Development, National Center for Child Health and Development, Tokyo, Japan; ²²Division of Clinical Pharmacology, Children's National Medical Center, Washington, DC, USA; ²³Departments of Pediatrics, Pharmacology & Physiology, George Washington University, School of Medicine and Health Sciences, Washington, DC, USA; ²⁴Department of Paediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel, Basel, Switzerland; ²⁵Paediatric Infectious Disease Unit, St George's Hospital, London, UK; ²⁶Department of Pharmacy, Shandong Provincial Qianfoshan Hospital, Shandong University, Jinan, China; ²⁷Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Shandong University, Jinan, China

*Corresponding author. Department of Pediatric Pharmacy, Shandong Provincial Qianfoshan Hospital Shandong University, 250014 Jinan, China. Tel: +86 (0)531 88383308; E-mail: zhao4wei2@hotmail.com

<https://orcid.org/0000-0002-1830-338X>

Received 5 December 2018; returned 29 January 2019; revised 26 February 2019; accepted 16 March 2019

Objectives: In the absence of consensus, the present meta-analysis was performed to determine an optimal dosing regimen of vancomycin for neonates.

Methods: A 'meta-model' with 4894 concentrations from 1631 neonates was built using NONMEM, and Monte Carlo simulations were performed to design an optimal intermittent infusion, aiming to reach a target AUC₀₋₂₄ of 400 mg·h/L at steady-state in at least 80% of neonates.

Results: A two-compartment model best fitted the data. Current weight, postmenstrual age (PMA) and serum creatinine were the significant covariates for CL. After model validation, simulations showed that a loading dose (25 mg/kg) and a maintenance dose (15 mg/kg q12h if <35 weeks PMA and 15 mg/kg q8h if ≥35 weeks PMA) achieved the AUC₀₋₂₄ target earlier than a standard 'Blue Book' dosage regimen in >89% of the treated patients.

Conclusions: The results of a population meta-analysis of vancomycin data have been used to develop a new dosing regimen for neonatal use and to assist in the design of the model-based, multinational European trial, NeoVanc.

Introduction

Vancomycin is one of the most widely used antibiotics for the treatment of serious Gram-positive infections. It is a high molecular weight complex glycopeptide that inhibits the cell wall synthesis of Gram-positive bacteria by the formation of stable complex murein pentapeptides, thereby causing inhibition of further peptidoglycan formation. It became the treatment of choice for staphylococcal infections when staphylococcal strains developed resistance to treatment with penicillin. It was then replaced by methicillin in the 1960s but, when the incidence of late-onset neonatal sepsis increased due to coagulase-negative and methicillin-resistant staphylococci, the use of vancomycin re-emerged and it is today the treatment of choice for many staphylococcal infections.^{1,2}

According to recent surveys,^{3–7} neonatal dosage recommendations for vancomycin are highly variable and include a range of single or multiple clinical factors, such as gestational age (GA), postnatal age (PNA), postmenstrual age (PMA), weight and creatinine clearance. Even internationally recognized dosing guidelines give different dosing recommendations, either as continuous (CVA) or intermittent intravenous (IVA) vancomycin administration. However, although vancomycin is one of the most studied antibiotics in neonates,^{2,8–10} population pharmacokinetic (popPK) and pharmacokinetic/pharmacodynamic (PK/PD) approaches have had limited success in leading to a clear consensus on the optimal dosing regimen to use in routine clinical practice. This is partly because the models and results are dependent on study/centre-related factors, including differences in the covariates that were incorporated in the final analysis. This study aimed to conduct a meta-analysis of published individual PK data and to build a popPK/PD model that would take into account all available variables, as part of the programme of work to plan the NeoVanc trial.¹¹

Methods

Identification of individual patient data

Published PK or PK/PD studies were identified through databases (PubMed, Embase) in 2014, according to the following screening criteria: PK study, vancomycin, neonates and infants, single and multicentre studies, all countries. The investigator responsible for the publication was contacted, invited to participate in the present study and provided individual vancomycin dose and concentration data and associated covariates. Additional, unpublished, routine therapeutic drug monitoring (TDM) data from our centre (Hôpital Robert Debré, Paris, France) were also used. All data were anonymized before transfer with a pre-defined data sharing agreement, according to Good Clinical and Laboratory Practices.

Requested covariates and individual information

The following data set of mandatory variables was collected to ensure that individual patient data could be included in the pooled model.

- Vancomycin administration information: dosing history for each infant (time of start of infusion, time of end of infusion and doses), continuous or intermittent infusion, vancomycin concentrations and exact sampling day and time.
- Demographic covariates: GA, PNA, birth weight, current weight (at sampling) and gender.

Table 1. Demographic characteristics of the 1631 neonates and infants included

Characteristic	Number (%)	Mean (SD)	Median (range)
Race			
Caucasian	1463 (89.7)		
Malaysian	116 (7.1)		
Japanese	52 (3.2)		
GA (weeks)		31.2 (5.0)	30.0 (22.3–42.1)
PMA (weeks)		33.3 (5.7)	32.0 (23.3–52.4)
PNA (days)		16 (15)	11 (1–90)
Current weight (g)		1785 (1127)	1350 (415–11370)
Serum creatinine (μmol/L)		59.2 (32.0)	53.9 (6.2–353.6)
Vancomycin treatment			
continuous infusion	295 (18.1)		
intermittent infusion	1336 (81.9)		

GA, gestational age; PMA, postmenstrual age; PNA, postnatal age.

- Information on co-medications was not collected and not analysed as it was available in only a limited number of neonates.
- Biological covariates: serum creatinine concentrations.
- Study-related covariates: analytical method used to quantify vancomycin (FPIA/EMIT, PENTINIA or CMIA/CLIA; see Table 2 for definitions), creatinine assay method (Jaffé or enzymatic) and corresponding units.

Data analysis

PK data were made available in a standard Microsoft Office Excel spreadsheet (CIC, 1426, Hôpital Robert Debré) and formatted for subsequent modelling using NONMEM V 7.2 (Icon Development Solutions, USA).

A first-order conditional estimation (FOCE) method with interaction was used to estimate PK parameters and their variability. One- and two-compartment models with first-order elimination were tested to estimate CL, central volume of distribution (V₁), peripheral volume of distribution (V₂) and intercompartmental clearance (Q) using the appropriate ADVAN sub-routines. Interindividual variability of the pharmacokinetic parameters was best described with an exponential model and was expressed as $\theta_i = \theta_{\text{mean}} \times e^{\eta_i}$, where θ_i represents the parameter value of the *i*th subject, θ_{mean} the typical value of the parameter in the population and η_i the variability between subjects, which is assumed to follow a normal distribution with a mean of zero and variance ω^2 .

Covariate analysis followed a forward and backward selection process. The likelihood ratio test was used to test the effect of each variable on model parameters. The effects of current weight, GA, PNA, PMA, serum creatinine concentration, analytical methods of vancomycin and creatinine, and ethnicity were investigated as potential covariates affecting PK parameters. During the first step of covariate model building, a covariate was included if a significant ($P < 0.05$, χ^2 distribution with one degree of freedom) decrease (reduction > 3.84) in the objective function value (OFV) from the basic model was obtained. All the significant covariates were then added simultaneously into a ‘full’ model. Subsequently, each covariate was independently removed from the full model. If the increase in the OFV was higher than 6.635 ($P < 0.01$, χ^2 distribution), the covariate was retained in the final model.

Model validation was based on graphical and statistical criteria. Goodness-of-fit plots, including observed (DV) versus population prediction (PRED), DV versus individual prediction (IPRED), conditional weighted residuals (CWRES) versus time and CWRES versus PRED were initially used for diagnostic purposes. The stability and performance of the final model were

Table 2. Studies included in the vancomycin meta-analysis

Study	No. of patients (N=1631)	PK study ^a	Administration	Location	Creatinine method	Vancomycin method	Citation
1	59	single centre	IVA	Glasgow, UK	Jaffé	FPIA	14
2	294	multicentre (4)	IVA	San Diego, CA, US	Jaffé	EMIT and FPIA	15
3	35	single centre	IVA	Glasgow, UK	Jaffé	FPIA	16
4	210	single centre	IVA	Leuven, Belgium	Jaffé	PETINIA	17
5	116	single centre	IVA	Kuala Lumpur, Malaysia	Jaffé	FPIA	18
6	66	single centre	CVA	Marseille, France	enzymatic	EMIT	19
7	61	single centre	CVA	Marseille, France	enzymatic	EMIT	20
8	125	single centre	IVA	Memphis, TN, US	enzymatic	EMIT	21
9	55	single centre	CVA	Glasgow, UK	enzymatic	CMIA	22
10	78	single centre	IVA	Paris, France	enzymatic	EMIT and FPIA	23
11	113	multicentre (3)	CVA	Paris, France	enzymatic	PETINIA and FPIA	24
12	199	single centre	IVA	Leuven, Belgium	enzymatic	PETINIA and FPIA	25
15	68	single centre	IVA	Tartu, Estonia	enzymatic	FPIA	26
13	52	single centre	IVA	Tokyo, Japan	enzymatic	CLIA	NP
14	100	single centre	IVA	Valencia, Spain	enzymatic	FPIA	NP

NP, not published; PETINIA, particle-enhanced turbidimetric inhibition immunoassay; FPIA, fluorescence polarization immunoassay method; EMIT, enzyme-multiplied immunoassay method; CMIA, chemiluminescent microparticle immunoassay; CLIA, chemiluminescent immunoassay. In our population, 1350 g, 32 weeks and 52 µmol/L are the median current weight (day of the study), postmenstrual age and serum creatinine concentration values, respectively.

^aNumber of centres is shown for multicentre studies.

also assessed by means of a non-parametric bootstrap with re-sampling and replacement. Re-sampling was repeated 200 times and the values of estimated parameters from the bootstrap procedure were compared with those estimated from the original data set. The entire procedure was performed in an automated fashion, using Perl-speaks-Nonmem (PsN v2.30). The final model was also evaluated graphically and statistically by normalized prediction distribution errors (NPDEs). One thousand data sets were simulated using the final population model parameters. NPDE results were summarized graphically by default as provided by the NPDE R package (v1.2): (i) QQ-plot of the NPDE; and (ii) histogram of the NPDE. The NPDE is expected to follow the N(0, 1) distribution.¹²

Monte Carlo simulations for dosage optimization were performed to evaluate different weight-adjusted (mg/kg) dosing regimens for three pre-defined neonatal groups: PMA <29, 29–35 and >35 weeks. Drug exposure was simulated 100 times for each set of patients including only the Caucasian patients. AUC between 0 and 24 h on the first treatment day (AUC_{0–24}) and AUC₂₄ at steady-state (AUC_{ss–24}) were calculated for each simulated patient. The parameter estimates obtained from the final model were used to estimate the target attainment rate for an AUC₂₄ of ≥400 mg·h/L with the standard dosage regimen recommended in the 'Blue Book'¹³ and to define the optimal dosing regimen able to attain this target in 80% of patients. The current dosage recommendations and a loading dose followed by a maintenance dose administered as an intermittent infusion were evaluated in the three PMA groups.

Results

Study population

A total of 1631 neonates and infants from 15 studies were included (Table 1). Their PMA and current weight (CW), expressed as means (SD) were 33.3 (5.7) weeks and 1785 (1127) g, respectively. An overview of the individual PK trials is presented in Table 2. We refer readers to the original studies for additional factual information.^{14–26}

Population PK analysis

Model building

A total of 4894 concentrations from 1631 patients were included in the population analysis. A two-compartment model with first-order elimination best fitted the data; both the OFV and the residual variability were lower than with a one-compartment model.

Covariate analysis

Allowing separate estimates for each analytical method in the residual variability caused a significant drop in the OFV of 113.5 units. Body weight was the most important clinical covariate following a systematic covariate analysis, associated with a drop in the OFV of 3367.1 units after incorporating it into the basic model using estimated allometric coefficients for CL, V₁ and V₂. A further decrease in the OFV of 244.5 units was achieved by including PMA on CL, and serum creatinine concentrations gave a further reduction (ΔOFV 1087.9 units). The model was further improved (ΔOFV 65.5 units) by introducing a conversion factor between the Jaffé and enzymatic assay methods for creatinine. Ethnicity (Malaysian patients) was identified as a sixth covariate (ΔOFV 302.1 units) on CL. The final model had the following structure:

$$CL = 0.0680 \times (CW/1350)^{0.863} \times RM \times RF \times F_{\text{Jaffé-Enzymatic}} \times F_{\text{Race}}$$

where CW is current weight, RM reflects renal maturation and RF reflects renal function. The population PK parameters of the final model are presented in Table 3.

Table 3. Population pharmacokinetic parameters of vancomycin and bootstrap results (n=500)

Parameters	Full data set		Bootstrap	
	final estimate	RSE (%)	median	2.5th–97.5th percentiles
Central volume of distribution V_1 (L) ^a				
θ_1	0.728	1.5	0.714	0.414–0.742
θ_2	1.13	3.0	1.12	0.596–1.200
Peripheral volume of distribution V_2 (L) ^b				
θ_3	0.358	11.1	0.335	0.185–0.474
θ_4	1.15	14.9	1.25	0.75–1.93
Intercompartment clearance Q (L/h) ^c				
θ_5	0.0301	12.5	0.0361	0.0248–1.190
Clearance CL (L/h) ^d				
θ_6	0.0680	1.3	0.0686	0.0664–0.0717
θ_7	0.863	5.3	0.895	0.787–0.968
$RM=(PMA/32)^{0.8}$				
θ_8	0.544	30.3	0.544	0.143–0.816
$RF=1/(F_{\text{Jaffé-Enzymatic}} \times CREA/54)^{0.9}$				
θ_9	0.666	3.6	0.655	0.598–0.718
$F_{\text{Jaffé-Enzymatic}}$				
θ_{10}	0.720	2.8	0.716	0.682–0.756
F_{race}				
θ_{11}	0.724	2.8	0.710	0.646–0.757
Interindividual variability (%)				
V_1	17.5	25.6	14.1	1.7–23.0
V_2	102.5	25.0	80.3	19.2–132.8
CL	18.2	21.6	15.2	2.2–21.0
Interoccasion variability (%)				
CL	19.1	20.1	16.7	2.4–22.7
Residual proportional (%)				
$FPIA$	22.2	4.8	22.2	19.9–24.2
$EMIT$	20.9	7.3	21.1	18.0–24.0
$PENTINIA$	25.1	5.6	24.7	21.7–27.8
$CMIA$	10.7	21.2	10.6	5.7–14.2
$CLIA$	38.3	25.8	39.2	19.6–58.5
Residual additive (mg/L)				
$FPIA$	1.57	7.7	1.63	1.32–1.99
$EMIT$	1.53	16.7	1.54	0.94–2.08
$PENTINIA$	1.01	19.6	1.06	0.59–1.65
$CMIA$	2.02	26.1	2.07	0.71–2.78
$CLIA$	3.30	28.7	3.26	0.73–4.97

CREA, serum creatinine concentration ($\mu\text{mol/L}$); PMA, postmenstrual age (weeks); RSE, residual standard error.

^a $V_1 = \theta_1 \times (CW/1350)^{0.2}$.

^b $V_2 = \theta_3 \times (CW/1350)^{0.4}$.

^c $Q = \theta_5 \times (CW/1350)$.

^d $CL = \theta_6 \times (CW/1350)^{0.7} \times RM \times RF \times F_{\text{Jaffé-Enzymatic}} \times F_{\text{race}}$.

Model evaluation

Model diagnostics showed acceptable goodness of fit for the final model. Predictions were unbiased, and no trends were observed in the diagnostic plots of CWRES versus time. The NPDE distribution and histogram were consistent with the theoretical $N(0, 1)$ distribution and density, indicating a good fit of the model to the individual data (Figure 1). The mean and variance of the NPDEs were 0.09 and 0.98, respectively. Visual predictive checks of the final model for all neonates and in subgroups of neonates <29 weeks (L),

29–35 weeks (M) and >35 weeks (H) are shown in Figure 2. The plots confirm that the average predicted concentrations matched the observed concentrations and that the variability was well estimated in the three subgroups.

In addition, the median PK parameter estimates resulting from the bootstrap procedure closely agreed with the respective values from the final population model, indicating that the final model was stable (Table 3).

Figure 1. Goodness-of-fit plots: (a) population predicted (PRED) versus observed concentrations (DV); (b) individual predicted (IPRED) versus DV; (c) conditional weighted residuals (CWRES) versus time; (d) CWRES versus PRED. Normalized prediction distribution errors (NPDE): (e) QQ-plot of the distribution of the NPDE versus the theoretical N (0, 1) distribution; (f) histogram of the distribution of the NPDE, with the density of the standard Gaussian distribution overlaid.

Dosing optimization

Dosing optimization was conducted in the Caucasian population. Monte Carlo simulations were performed to evaluate different mg/kg dosing regimens for the three neonatal groups.

With the standard vancomycin dosing regimen at steady-state, the percentage of neonates reaching the target AUC_{ss-24} of ≥ 400 mg·h/L was 74.0% and the percentage exposed to an $AUC_{ss-24} > 700$ mg·h/L was 23.0% when considering all age

Figure 2. Validation of the model by use of a visual predictive check (VPC). VPC after (a) continuous (CVA) and (b) intermittent (IVA) vancomycin administration. Comparison of the 5th (bottom dashed line), 50th (solid line) and 95th (top dashed line) percentiles obtained from 1000 simulations and the observed data (circles) for vancomycin concentrations in premature neonates <29 weeks (L), 29–35 weeks (M) and >35 weeks (H). Open circles represent individual observed concentrations.

groups. When considering only neonates <29 weeks PMA, the corresponding values fell to 27.7% and 1.1%, respectively (Table 4).

With a loading dose of 25 mg/kg followed by the optimal maintenance dose of 15 mg/kg, either q12h if ≤ 35 weeks PMA or q8h if >35 weeks PMA, the percentage of neonates reaching the target

AUC_{ss-24} of 400 mg·h/L was 89.3%, while the percentage exposed to an $AUC_{ss-24} > 700$ mg·h/L was 33.3% when considering all age groups. When considering only neonates <29 weeks PMA, the corresponding values increased to 95.0% and 45.5%, respectively (Table 5).

Figure 2. Continued.

The target attainment rate on the first day of treatment increased from 42.6% with the standard regimen to 88.9% with the loading dose strategy.

Discussion

To the best of our knowledge, this is the largest meta-analysis that has assessed the population PK of vancomycin in neonates and

young infants aged <3 months. The analysis has combined vancomycin concentrations linked to key demographic and biological covariates from 15 PK studies conducted in seven different countries. Monte Carlo simulations showed that the current dosage regimen was not suitable for the treatment of staphylococcal infection and that the optimal vancomycin dosing regimen should include a loading dose of 25 mg/kg for all neonates, irrespective of their PMA, followed by a maintenance dose adapted to their PMA.

Table 4. Monte Carlo simulations of vancomycin standard dose regimen^a

Characteristic	PMA (weeks)			Total
	<29	29–35	>35	
Number of patients	335	618	510	1463 ^b
Standard dose regimen (mg/kg)	15 (q24h)	15 (q12h)	15 (q8h)	
First day				
AUC _{0–24} median (mg·h/L)	246	378	495	385
AUC _{0–24} 5th–95th (mg·h/L)	163–356	264–523	332–725	203–638
Target attainment rate (%)	1.5	39.0	81.0	45.1
AUC _{0–24} 400–700 mg·h/L (%)	1.5	38.9	74.0	42.6
AUC _{0–24} >700 mg·h/L (%)	0	0.1	7.0	2.5
AUC _{0–24} >800 mg·h/L (%)	0	0	2.0	0.7
C _{min24} median (mg/L)	3.8	9.0	14.3	9.0
C _{min24} 5th–95th (mg·h/L)	0.2–8.7	2.9–18.4	4.8–30.8	1.6–24.0
C _{min24} >20 mg/L (%)	0	3.4	24.2	9.9
Steady-state				
AUC _{ss–24} median (mg·h/L)	338	536	654	520
AUC _{ss–24} 5th–95th (mg·h/L)	203–547	323–893	368–1276	259–1028
Target attainment rate (%)	27.7	84.3	91.9	74.0
AUC _{ss–24} 400–700 mg·h/L (%)	26.6	65.5	49.4	51.0
AUC _{ss–24} >700 mg·h/L (%)	1.1	18.7	42.5	23.0
AUC _{ss–24} >800 mg·h/L (%)	0.5	10.0	29.6	14.7
C _{minss–24} median (mg/L)	6.0	12.3	17.2	11.9
C _{minss–24} 5th–95th (mg·h/L)	1.1–14.7	4.1–28.3	5.6–46.0	2.8–34.4
C _{minss–24} >20 mg/L (%)	12.8	17.6	40.0	21.7

AUC_{0–24}, 24 h AUC at the first day; C_{min24}, trough level at the first day; AUC_{ss–24}, 24 h AUC at steady-state; C_{minss–24}, trough level at steady-state.

^aAs indicated in the Blue Book.¹²

^bNumber of Caucasian patients.

Although widely used for many years, important questions remain on how to optimize vancomycin dosing in neonates.^{2,8,9} In the absence of prospective evaluation, most neonatal units have developed local dosing recommendations, resulting in variable exposures that may lead to poor efficacy, induction of resistance or toxicity.³ Consequently, vancomycin dosage regimens adapted to neonates require harmonization, taking into account the impact of developmental pharmacology on disposition and PK parameters from very preterm neonates through term neonates to older children.²⁷ This issue is central, and initiatives from both the FDA and EMA are currently being undertaken to revise vancomycin dosing.^{28,29}

Drug PK and PD need to be linked to explicate individual characteristics whether constitutional (age, weight, genetics, etc.) or environmental (pathology, drug interactions, etc.). In this context, population modelling allows assessment and quantification of sources of variability in drug exposure and response in the target population, even under sparse sampling conditions.^{30–32} The present study has confirmed the impact of serum creatinine and vancomycin assay methods as predictors of vancomycin concentrations in neonates.^{33,34} Additional covariates, such as ventilation,³⁵ co-administered drugs³⁶ (e.g. aminoglycosides or ibuprofen), extracorporeal membrane oxygenation (ECMO)³⁷ and whole body cooling,³⁸ as well as centre- or country-dependent effects linked to ethnic, environmental and nutritional differences, were not

explored in the current study, as they were not available in all data sets. However, it is recognized that they may also contribute to PK variability in neonates.

Model-based approaches to characterize drug PK/PD have been recommended as powerful tools for overcoming the practical and ethical challenges associated with dose selection for neonatal indications.^{39,40} For vancomycin, a model tailored dose had already been demonstrated to increase substantially the target attainment rate of vancomycin in treated neonates.¹⁰ However, there were few neonates of <29 weeks gestational age in that study, and centre-based effects could not be eliminated. These limitations were addressed in the present PK meta-analysis, which was conducted by pooling 4894 vancomycin concentrations from 1631 neonates. Although robust parameter estimates were obtained with this strategy, different strategies may be necessary when data are heterogeneous.⁴¹

For vancomycin, exposure, measured by AUC_{0–24}, is the PK/PD parameter influencing efficacy and emergence of resistance,^{42–44} but also influencing toxicity. Nephrotoxicity is a multifactorial, well-identified risk of high vancomycin exposure and high trough concentrations.⁴⁵ AUC_{0–24} or corresponding trough levels can vary widely and independently, since the trough depends on both the daily dose and the frequency of administration, whereas AUC_{0–24} only depends on the daily dose. Consequently, in the present study, simulations were performed to evaluate the current

Table 5. Monte Carlo simulation of vancomycin dosage regimen with a loading dose 25 mg/kg following by optimal maintenance dose

Characteristics	PMA (weeks)			Total
	<29	29–35	>35	
Number of patients	335	618	510	1463
Loading dose (mg/kg)	25	25	25	
Optimal maintenance dose (mg/kg)	15 (q12h)	15 (q12h)	15 (q8h)	
First day				
AUC _{0–24} median (mg·h/L)	559	492	596	539
AUC _{0–24} 5th–95th (mg·h/L)	384–787	336–692	426–820	358–812
Target attainment rate (%)	87.8	83.0	93.2	88.9
AUC _{0–24} 400–700 mg·h/L (%)	74.0	78.6	67.5	74.7
AUC _{0–24} >700 mg·h/L (%)	13.7	4.4	25.7	14.2
AUC _{0–24} >800 mg·h/L (%)	4.1	1.0	12.0	5.6
C _{min24} median (mg/L)	14.4	10.7	15.5	13
C _{min24} 5th–95th (mg·h/L)	5.3–28.0	3.6–22.5	5.2–34.7	4.3–29.0
C _{min24} >20 mg/L (%)	21.2	8.9	31.3	19.8
Steady-state				
AUC _{ss–24} median (mg·h/L)	677	529	656	600
AUC _{ss–24} 5th–95th (mg·h/L)	401–1102	325–883	368–1293	348–1093
Target attainment rate (%)	95.0	83.5	92.5	89.3
AUC _{ss–24} 400–700 mg·h/L (%)	49.5	65.0	49.4	56.0
AUC _{ss–24} >700 mg·h/L (%)	45.5	17.6	43.1	33.3
AUC _{ss–24} >800 mg·h/L (%)	28.9	9.0	30.3	21.0
C _{minss–24} median (mg/L)	17.5	12.2	17.5	15
C _{minss–24} 5th–95th (mg·h/L)	6.5–38.0	4.0–28.5	5.6–46.1	4.9–37.6
C _{minss–24} >20 mg/L (%)	39.3	17.6	41.5	30.9

dosage regimen¹³ and to optimize efficacy by determining the target attainment rate and exposure to vancomycin measured by the AUC_{0–24}. A target AUC_{0–24} of at least 400 mg·h/L was selected because an AUC_{0–24}/MIC ratio of 400 has been associated with favourable treatment outcomes in adults, assuming that bacterial strains have a vancomycin MIC ≤1 mg/L.^{43,46} Simulations of the current dosage recommendation (see Table 5) were performed after the first dose and at steady-state. Our results showed that the current daily dose was too low for all neonatal age groups but particularly for neonates <29 weeks, as <30% of neonates reached the steady-state target. As a loading dose strategy is recommended in adult settings in order to reduce the time needed to reach the target AUC_{0–24},^{47,48} simulations were then performed with a loading dose and optimal maintenance doses in all age groups, based on weight and PMA. Increasing the maintenance dose to 15 mg/kg q12h instead of q24h was also tested in the group <29 PMA weeks to optimize dosage. These modifications led to an increase in the target attainment rate after the first dose and at steady-state in all age groups.

Nephrotoxicity is a recognized side effect of vancomycin treatment, although its safety profile is considered favourable. The risk of nephrotoxicity primarily increases with high vancomycin exposure and duration of administration.^{45,49} In studies in adults and children,⁴⁵ reported incidence varied widely, from 5% to 43%, occurrence increased with longer durations of

administration with a range of 4.3–17 days and nephrotoxicity was reversible in the majority of cases. In neonates, most studies were not sufficiently powered to detect nephrotoxicity and, when reported, renal impairment was frequently associated with concomitant administration of nephrotoxic drugs.⁵⁰

Therefore, optimizing exposure while reducing duration of administration would maximize clinical efficacy while minimizing toxicity and selection of resistance.

The upper AUC₂₄ limit remains a matter of debate. ‘Usual’ AUC₂₄ values of 700 or 800 mg·h/L have been used in both adults^{46,51,52} and children;⁴⁸ however, more extreme values have also been reported, with breakpoints for nephrotoxicity of <600 or >1300 mg·h/L.^{51,53} In the absence of specific neonatal data, a value of 700 mg·h/L was used in the present study. With our simulated dosage regimen, 89% of neonates reached the predetermined AUC_{ss–24} target and 21.0% had an AUC_{ss–24} >800 mg·h/L; this was slightly higher than the percentage expected with the dosing regimen that is currently used. Additional TDM is necessary to individualize therapy for patients at risk of high exposure rates.

The simulated drug regimens presented here in the different neonatal age groups resulted in higher percentages of patients who would reach the target for efficacy but also higher percentages of patients who would have vancomycin concentrations over the nephrotoxicity threshold of 15–20 mg/L, reported both in adults and in children.^{24,54,55} This potential higher risk of

nephrotoxicity requires further evaluation but, in our recent patient-tailored vancomycin dose study in 190 neonates, no patient developed nephrotoxicity after model-based TDM although the AUC₀₋₂₄ reached 1200 mg·h/L in some patients.¹⁰

The simulated vancomycin regimens were developed as the preclinical component of the FP7 NeoVanc programme. As our final objective is to maximize clinical efficacy and minimize toxicity and selection of resistance by increasing exposure and reducing length of treatment, our data are now being taken forward in a randomized controlled trial (RCT) of the optimized regimen in which the duration of vancomycin is reduced to 5 days, compared with a standard regimen administered for 10 days. The NeoVanc RCT was evaluated by experts at the European Commission, a paediatric Investigation Plan was validated by the EMA and regulatory authorities, and a Data Safety and Monitoring Board closely monitors patients and data. Owing to multifactorial variability in vancomycin disposition, drug monitoring is being performed in patients included in the two arms to further guide dosing,⁵⁶ although a trough level is not a very good predictor of AUC₂₄.^{57,58} Our RCT will also provide information on additional factors specific to neonates that may contribute to toxicity, including hypovolaemia and concurrent nephrotoxic drug use.

Acknowledgements

We thank members of WP3 of the NeoVanc project (Dr Aude Facchin, Dr Pauline Lancia and Dr Virginia Neyro; Department of Pediatric Pharmacology and Pharmacogenetics, Hôpital Robert Debré, AP-HP, Paris, France) for participating in the population PK analysis and literature review on vancomycin toxicity.

The following members of NeoVanc participated in the discussions on our PK results, on selection of target for simulations and use in the NeoVanc trial: Professor Mike Sharland (St George's Hospital Medical School, London, UK), Professor Irja Lutsar (Tartu Ulikool, Estonia), Dr V. Ramos and Professor W. Hope (University of Liverpool, UK).

Funding

This study was supported by The European Seven Framework programme – Health.2013.4.2-1. Project acronym: NeoVanc – Grant Agreement number: 602041. W. Z. received additional funding from China National Science and Technology Major Projects for ‘Major New Drugs Innovation and Development’ (2017ZX09304029-002).

Transparency declarations

None to declare.

Author contributions

E. J.-A., W. Z., S. L. and M. S. designed the research; K. A., E. V. C., V. B., A. H. T., N. S., B. M., Y.-L. L., R. M., J.-E. P., I. L., J. S., H. N. and J. N. A. provided data and revised the manuscript; W. Z. and S. L. analysed the data; E. J.-A. wrote the first version of the manuscript; E. J.-A., W. Z., A. H. T., I. L. and M. S. revised the manuscript.

References

1 de Hoog M, Mouton JW, van den Anker JN. Vancomycin: pharmacokinetics and administration regimens in neonates. *Clin Pharmacokinet* 2004; **43**: 417–40.

2 Jacqz-Aigrain E, Zhao W, Sharland M *et al*. Use of antibacterial agents in the neonate: 50 years of experience with vancomycin administration. *Semin Fetal Neonatal Med* 2013; **18**: 28–34.

3 Leroux S, Zhao W, Bétrémieux P *et al*. Therapeutic guidelines for prescribing antibiotics in neonates should be evidence-based: a French national survey. *Arch Dis Child* 2015; **100**: 394–8.

4 Gharbi M, Doerholt K, Vergnano S *et al*. Using a simple point-prevalence survey to define appropriate antibiotic prescribing in hospitalised children across the UK. *BMJ Open* 2016; **3**: e012675.

5 Metsvaht T, Nellis G, Verandi H *et al*. High variability in the dosing of commonly used antibiotics revealed by a Europe-wide point prevalence study: implications for research and dissemination. *BMC Pediatr* 2015; **15**: 41–51.

6 Kadambari S, Heath PT, Sharland M *et al*. Variation in gentamicin and vancomycin dosage and monitoring in UK neonatal units. *J Antimicrob Chemother* 2011; **66**: 2647–50.

7 Osowicki J, Gwee A, Noronha J *et al*. Australia-wide point prevalence survey of antimicrobial prescribing in neonatal units: how much and how good? *Pediatr Inf Dis J* 2015; **34**: e185–90.

8 Jacqz-Aigrain E, Leroux S, Zhao W *et al*. How to use vancomycin optimally in neonates: remaining questions. *Expert Rev Clin Pharmacol* 2015; **8**: 635–48.

9 De Cock RF, Allegaert K, Brussee JM *et al*. Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: towards a semi-physiological function for maturation in glomerular filtration. *Pharm Res* 2014; **31**: 2643–54.

10 Leroux S, Jacqz-Aigrain E, Biran V *et al*. Clinical utility and safety of a model-based patient-tailored dose of vancomycin in neonates. *Antimicrob Agents Chemother* 2016; **60**: 2039–42.

11 FP7 Vancomycin trial NeoVanc. www.neovanc.org.

12 Comets E, Brendel K, Mentre F. Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: the npde add-on package for R. *Comput Methods Programs Biomed* 2008; **90**: 154–66.

13 Sharland M. *Manual of Childhood Infections. The Blue Book*. Oxford: Oxford University Press, 2011.

14 Grimsley C, Thomson AH. Pharmacokinetics and dose requirements of vancomycin in neonates. *Arch Dis Child Fetal Neonatal Ed* 1999; **81**: F221–7.

15 Capparelli EV, Lane JR, Romanowski GL *et al*. The influences of renal function and maturation on vancomycin elimination in newborns and infants. *J Clin Pharmacol* 2001; **41**: 927–34.

16 Thomson AH, Sie A. Prospective evaluation of neonatal vancomycin dosage guidelines and population parameter estimates. *Paediatr Perinat Drug Ther* 2003; **5**: 116–23.

17 Anderson BJ, Allegaert K, Van den Anker JN *et al*. Vancomycin pharmacokinetics in preterm neonates and the prediction of adult clearance. *Br J Clin Pharmacol* 2007; **63**: 75–84.

18 Lo YL, van Hasselt JG, Heng SC *et al*. Population pharmacokinetics of vancomycin in premature Malaysian neonates: identification of predictors for dosing determination. *Antimicrob Agents Chemother* 2010; **54**: 2626–32.

19 Oudin C, Vialat R, Boulamery A *et al*. Vancomycin prescription in neonates and young infants: toward a simplified dosage. *Arch Dis Child Fetal Neonatal Ed* 2011; **96**: F365–70.

20 Marsot A, Vialat R, Boulamery A *et al*. Vancomycin: predictive performance of a population pharmacokinetic model and optimal dose in neonates and young infants. *Clin Pharmacol Drug Dev* 2012; **1**: 144–51.

21 Mehrotra N, Tang L, Phelps SJ *et al*. Evaluation of vancomycin dosing regimens in preterm and term neonates using Monte Carlo simulations. *Pharmacotherapy* 2012; **32**: 408–19.

22 Patel AD, Anand D, Lucas C *et al*. Continuous infusion of vancomycin in neonates. *Arch Dis Child* 2013; **98**: 478–9.

- 23 Zhao W, Kaguelidou F, Biran V *et al.* External evaluation of population pharmacokinetic models of vancomycin in neonates: the transferability of published models to different clinical settings. *Br J Clin Pharmacol* 2013; **75**: 1068–80.
- 24 Zhao W, Lopez E, Biran V *et al.* Vancomycin continuous infusion in neonates: dosing optimisation and therapeutic drug monitoring. *Arch Dis Child* 2013; **98**: 449–53.
- 25 Samardzic J, Smits A, Spriet I *et al.* Different vancomycin immunoassays contribute to the variability in vancomycin trough measurements in neonates. *Biomed Res Int* 2016; **2016**: 1974972.
- 26 Padari H, Oselin K, Tasa T *et al.* Coagulase negative staphylococcal sepsis in neonates: do we need to adapt vancomycin dose or target? *BMC Pediatr* 2016; **16**: 206.
- 27 Kearns GL, Abdel-Rahman SM, Alander SW *et al.* Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; **349**: 1157–67.
- 28 EMA. EMA recommends changes to prescribing information for vancomycin antibiotics. Last update 17/11/2017. https://www.ema.europa.eu/en/documents/referral/vancomycin-article-31-referral-ema-recommends-changes-prescribing-information-vancomycin-antibiotics_en.pdf.
- 29 Vancomycin Hydrochloride for Injection, USP. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/062911s0351bl.pdf.
- 30 Tod M, Jullien V, Pons G. Facilitation of drug evaluation in children by population methods and modelling. *Clin Pharmacokinet* 2008; **47**: 231–43.
- 31 Vermeulen E, van den Anker JN, Della Pasqua O *et al.*; Global Research in Paediatrics (GRiP). How to optimise drug study design: pharmacokinetics and pharmacodynamics studies introduced to paediatricians. *J Pharm Pharmacol* 2017; **69**: 439–47.
- 32 Leroux S, Turner MA, Guellec CB *et al.* Pharmacokinetic studies in neonates: the utility of an opportunistic sampling design. *Clin Pharmacokinet* 2015; **54**: 1273–85.
- 33 Zhao W, Jacqz-Aigrain E. The importance of knowing how vancomycin is measured when interpreting its pharmacokinetic results. *Ther Drug Monit* 2013; **35**: 416.
- 34 Oyaert M, Peermans N, Kieffer D *et al.* Novel LC-MS/MS method for plasma vancomycin: comparison with immunoassays and clinical impact. *Clin Chim Acta* 2015; **441**: 63–70.
- 35 Medellín-Garibay SE, Romano-Moreno S, Tejedor-Prado P *et al.* Influence of mechanical ventilation on the pharmacokinetics of vancomycin administered by continuous infusion in critically ill patients. *Antimicrob Agents Chemother* 2017; **61**: e01249–17.
- 36 Constance JE, Balch AH, Stockmann C *et al.* A propensity-matched cohort study of vancomycin-associated nephrotoxicity in neonates. *Arch Dis Child Fetal Neonatal Ed* 2016; **101**: F236–43.
- 37 Donatello K, Roberts JA, Cristallini S *et al.* Vancomycin population pharmacokinetics during extracorporeal membrane oxygenation therapy: a matched cohort study. *Crit Care* 2014; **18**: 632.
- 38 de Haan TR, Bijleveld YA, van der Lee JH *et al.* Pharmacokinetics and pharmacodynamics of medication in asphyxiated newborns during controlled hypothermia. The PharmaCool multicenter study. *BMC Paediatr* 2012; **12**: 45.
- 39 Rathi C, Lee RE, Meibohm B. Translational PK/PD of anti-infective therapeutics. *Drug Discov Today Technol* 2016; **21–22**: 41–9.
- 40 Admiraal R, van Kesteren C, Boelens JJ *et al.* Towards evidence-based dosing regimens in children on the basis of population pharmacokinetic pharmacodynamic modelling. *Arch Dis Child* 2014; **99**: 267–72.
- 41 Svensson E, van der Walt JS, Barnes KI *et al.* Integration of data from multiple sources for simultaneous modelling analysis: experience from nevirapine population pharmacokinetics. *Br J Clin Pharmacol* 2012; **74**: 465–76.
- 42 Ruback M, Lomaestro B, Rotschafer JC *et al.* Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 2009; **66**: 82–98.
- 43 Sakoulas G, Moise-Broder PA, Schentag J *et al.* Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol* 2004; **42**: 2398–402.
- 44 Mouton JW, Brown DF, Apfalter P *et al.* The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach. *Clin Microbiol Infect* 2012; **18**: E37–45.
- 45 van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother* 2013; **57**: 734–44.
- 46 Pappas PG, Kauffman CA, Anders DR *et al.* *Clin Infect Dis* 2009; **48**: 503–35.
- 47 Álvarez O, Plaza-Plaza JC, Ramirez M *et al.* Pharmacokinetic assessment of vancomycin loading dose in critically ill patients. *Antimicrob Agents Chemother* 2017; **61**: e00280–17.
- 48 Le J, Ny P, Capparelli E *et al.* Pharmacodynamic characteristics of nephrotoxicity associated with vancomycin use in children. *J Pediatric Infect Dis Soc* 2015; **4**: e109–16.
- 49 Filippone EJ, Kraft WK, Farber JL. The nephrotoxicity of vancomycin. *Clin Pharmacol Ther* 2017; **102**: 459–69.
- 50 Lestner JM, Hill LF, Heath PT *et al.* Vancomycin toxicity in neonates: a review of the evidence. *Curr Opin Infect Dis* 2016; **29**: 237–47.
- 51 Suzuki Y, Kawasaki K, Sato Y *et al.* Is peak concentration needed in therapeutic drug monitoring of vancomycin? A pharmacokinetic-pharmacodynamic analysis in patients with methicillin-resistant *Staphylococcus aureus* pneumonia. *Chemotherapy* 2012; **58**: 308–12.
- 52 Zasowski EJ, Murray KP, Trinh TD *et al.* Identification of vancomycin exposure-toxicity thresholds in hospitalized patients receiving intravenous vancomycin. *Antimicrob Agents Chemother* 2017; **62**: e01684–17.
- 53 Lodise TP, Patel N, Lomaestro BM *et al.* Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis* 2009; **49**: 507–14.
- 54 Labreche MJ, Graber CJ, Nguyen HM. Recent updates on the role of pharmacokinetics-pharmacodynamics in antimicrobial susceptibility testing as applied to clinical practice. *Clin Infect Dis* 2015; **61**: 1446–52.
- 55 Zhao W, Leroux S, Jacqz-Aigrain E. Dosage individualization in children: integration of pharmacometrics in clinical practice. *World J Pediatr* 2014; **10**: 197–203.
- 56 Finch NA, Zasowski EJ, Murray KP *et al.* A quasi-experiment to study the impact of vancomycin area under the concentration-time curve-guided dosing on vancomycin-associated nephrotoxicity. *Antimicrob Agents Chemother* 2017; **22**: e01293–17.
- 57 Neely MN, Youn G, Jones B *et al.* Are vancomycin trough concentrations adequate for optimal dosing? *Antimicrob Agents Chemother* 2014; **58**: 309–16.
- 58 Hale CM, Seabury RW, Steele JM *et al.* Are vancomycin trough concentrations of 15 to 20 mg/L associated with increased attainment of an AUC/MIC ≥ 400 in patients with presumed MRSA infection? *J Pharm Pract* 2017; **30**: 329–35.