Received: 6 November 2023 | Revised: 18 January 2024 | Accepted: 31 January 2024

DOI: 10.1111/bcp.16026

ORIGINAL ARTICLE

Population pharmacokinetics of vancomycin in term neonates with perinatal asphyxia treated with therapeutic hypothermia

Marlotte A. A. van der Veer[1] | Timo R. de Haan[2] | Linda G. W. Franken[1] | Reinier M. van Hest[1] | Floris Groenendaal[3,4] | Peter H. Dijk[5] | Willem P. de Boode[6] | Sinno Simons[7] | Koen P. Dijkman[8] | Henrica L. M. van Straaten[9] | Monique Rijken[10] | Filip Cools[11] | Debbie H. G. M. Nuytemans[2] | Anton H. van Kaam[2] | Yuma A. Bijleveld[1] | Ron A. A. Mathôt[1] | for the PharmaCool Study Group

[1]Department of Pharmacy & Clinical Pharmacology, Amsterdam University Medical Center, Amsterdam, The Netherlands

[2]Department of Neonatology, Emma Children's Hospital, Amsterdam University Medical Center, Amsterdam, The Netherlands

[3]Department of Neonatology, Wilhelmina Children's Hospital, Utrecht, The Netherlands

[4]UMC Utrecht Brain Center, University Medical Center Utrecht and Utrecht University, Utrecht, The Netherlands

[5]University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatrics, Division of Neonatology, University of Groningen, Groningen, The Netherlands

[6]Department of Neonatology, Radboud University Medical Center, Radboud Institute for Health Sciences, Amalia Children's Hospital, Nijmegen, The Netherlands

[7]Department of Neonatal and Pediatric Intensive Care, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

[8]Department of Neonatology, Máxima Medical Center Veldhoven, Veldhoven, The Netherlands

[9]Department of Neonatology, Isala Clinics, Zwolle, The Netherlands

[10]Department of Neonatology, Willem-Alexander Children's Hospital, Leiden University Medical Center, Leiden, The Netherlands

[11]Department of Neonatology, Vrije Universiteit Brussel, Brussels, Belgium

Correspondence
Marlotte A. A. van der Veer, Department of Pharmacy & Clinical Pharmacology, Amsterdam University Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Email: m.a.a.vanderveer@amsterdamumc.nl

Funding information
This study was funded by the Dutch government (ZonMw grant number 40-41500-98-9002).

Aims: Little is known about the population pharmacokinetics (PPK) of vancomycin in neonates with perinatal asphyxia treated with therapeutic hypothermia (TH). We aimed to describe the PPK of vancomycin and propose an initial dosing regimen for the first 48 h of treatment with pharmacokinetic/pharmacodynamic target attainment.

Methods: Neonates with perinatal asphyxia treated with TH were included from birth until Day 6 in a multicentre prospective cohort study. A vancomycin PPK model was constructed using nonlinear mixed-effects modelling. The model was used to evaluate published dosing guidelines with regard to pharmacokinetic/pharmacodynamic target attainment. The area under the curve/minimal inhibitory concentration ratio of 400–600 mg*h/L was used as target range.

Results: Sixteen patients received vancomycin (median gestational age: 41 [range: 38–42] weeks, postnatal age: 4.4 [2.5–5.5] days, birth weight: 3.5 [2.3–4.7] kg), and 112 vancomycin plasma concentrations were available. Most samples (79%) were

The authors confirm that the principal investigator for this paper is T.R. de Haan.

collected during the rewarming and normothermic phase, as vancomycin was rarely initiated during the hypothermic phase due to its nonempirical use. An allometrically scaled 1-compartment model showed the best fit. Vancomycin clearance was 0.17 L/h, lower than literature values for term neonates of 3.5 kg without perinatal asphyxia (range: 0.20–0.32 L/h). Volume of distribution was similar. Published dosing regimens led to overexposure within 24 h of treatment. A loading dose of 10 mg/kg followed by 24 mg/kg/day in 4 doses resulted in target attainment.

Conclusion: Results of this study suggest that vancomycin clearance is reduced in term neonates with perinatal asphyxia treated with TH. Lower dosing regimens should be considered followed by model-informed precision dosing.

KEYWORDS

antimicrobial therapy, neonates, perinatal asphyxia, pharmacokinetics, therapeutic hypothermia, vancomycin

1 | INTRODUCTION

The glycopeptide **vancomycin** is frequently used to treat neonatal nosocomial Gram-positive infections such as methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci infections.[1] Dosing of vancomycin in neonates is complex, primarily due to its notable interindividual variability (IIV), arising from the intricate interplay between body size, organ maturation and function, and the drug's narrow therapeutic range.[2] Overexposure to vancomycin could result in nephrotoxicity, while underexposure might lead to treatment failure.[3] This challenge might be particularly pronounced in neonatal populations presenting with a compromised renal function, such as neonates with perinatal asphyxia who are treated with controlled therapeutic hypothermia (TH) because of hypoxic–ischaemic encephalopathy. Suboptimal treatment or iatrogenic kidney damage in these critically ill neonates, who already may suffer from multiple organ failure (MOF) as a result of perinatal asphyxia, should be avoided.[4] The incidence of MOF in neonates with perinatal asphyxia treated with TH is 47%.[5] Performing model-informed precision dosing (MIPD) for vancomycin is therefore urgently needed in this group of neonates with perinatal asphyxia so that the vancomycin dose can be tailored towards an exposure where both the risk for treatment failure and nephrotoxicity are minimized. However, it necessitates the use of an appropriate population pharmacokinetic (PPK) model specifically developed for these neonates and entails some turnaround time. Relying on appropriate guidelines is crucial for the initial dosing regimen, which needs to achieve target exposure in the first 24 h of treatment in ideally 90% of neonates, but without ending up with under- or overexposure. However, there is no consensus on the best vancomycin dosing approach for neonates overall,[6] and dosing recommendations for neonates with perinatal asphyxia treated with TH are lacking. It remains uncertain if existing dosing guidelines would result in adequate or excessive exposure to vancomycin in neonates with perinatal asphyxia.

What is already known about this subject

- Dosing adjustments are needed for various renally cleared antibiotics when administrated to (near) term neonates with perinatal asphyxia and treated with therapeutic hypothermia, as there is substantial evidence indicating reduced drug clearance.
- There is a notable absence of studies examining the clearance of vancomycin, a glycopeptide characterized by a narrow therapeutic range, in this neonatal population.

What this study adds

- Vancomycin clearance is reduced in neonates with perinatal asphyxia treated with therapeutic hypothermia compared to those without perinatal asphyxia treated with therapeutic hypothermia.
- Conventional dosing regimens result in excessive vancomycin exposure, necessitating a more conservative dosing approach to mitigate the risk of unwanted side-effects.

To the best of our knowledge, nothing is known about the PPK of vancomycin in this specific population. The aim of the current study is to describe the PPK of vancomycin in (near) term neonates with perinatal asphyxia treated with TH and to propose an optimized initial dosing regimen for the first 48 h of vancomycin treatment with PK/pharmacodynamic (PD) target attainment.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This study is a retrospective PPK data analysis of prospectively collected data within the PharmaCool study.[7] The PharmaCool study was a large multicentre prospective observational cohort study conducted in all 10 Dutch and 2 Belgian neonatal intensive care units (NICUs), investigating the impact of TH on various drugs in neonates with perinatal asphyxia (https://trialsearch.who.int/Trial2.aspx?TrialID=NTR2529). Whole-body TH aims to improve long term neurodevelopment outcome by lowering and stabilizing core body temperature to 33.5°C for 72 h within 6 h of the hypoxic–ischaemic incident, after which neonates are slowly rewarmed to normothermia (36.5°C).[8] (Near) term neonates (gestational age [GA] > 36 weeks) with perinatal asphyxia who underwent TH were included in this study from birth until the 6th day of life. Criteria for exclusion encompassed the existence of congenital hepatic or renal pathology, absence of central venous or arterial access for sample collection or lack of parental consent. The study design has been described in detail elsewhere.[7]

2.2 | Data and sample collection

Patient specific-, demographic-, clinical- and laboratory data were collected for each patient: GA, postmenstrual age (PMA), postnatal age (PNA), birth weight, sex, Thompson score, Apgar score, cause of asphyxia, extent and duration of resuscitation, need for ventilator and/or cardiovascular support, co-medication, mean daily urinary output, serum creatinine (SCr), urea, aspartate aminotransferase, alanine aminotransferase, and the presence of MOF. The latter was defined as the presence of failure in renal- or liver function, as per the criteria outlined by Shah et al., and in accordance with previous studies.[9–11] Renal involvement was based on the presence of at least 1 of the following criteria: (i) anuria or oliguria (<1 mL/kg/h) for 24 h or longer and a SCr concentration >100 mmol/L; (ii) anuria or oliguria for >36 h; (iii) any SCr concentration >125 mmol/L; or (iv) serial SCr levels that increased postnatally. Vancomycin was prescribed as a second-line antibiotic for all patients based on positive blood cultures and dosed according to the Dutch paediatric formulary (www.kinderformularium.nl) at time of enrolment or local treatment protocol as standard of care (which ranged from 20 to 30 mg/kg/day in 2 divided doses), and adjusted based on vancomycin trough levels following local protocols.[12]

At fixed points during hypothermia (Days 2 and 3), rewarming (Day 4) and normothermia (Day 5), blood samples were collected from indwelling arterial lines.[7] Vancomycin plasma samples were analysed using a validated liquid–chromatography mass-spectrometry as previously described.[13] In short, the accuracy at the lowest limit of quantitation (1.0 mg/L) was 104%, with an imprecision of 11.5%. For the middle level of quantification (40.0 mg/L), accuracy was 99.7%, and imprecision was 2.1%. At the upper limit of quantification (100.0 mg/L), accuracy and imprecision were 101.7 and 4.9%, respectively. The analysis required only 25 μL of plasma.

2.3 | Development of PPK model

Vancomycin concentration data were analysed using the first-order conditional estimation with interaction (FOCE-I) algorithm as implemented in the nonlinear-mixed-effects modelling software NONMEM (version 7.4.2, ICON Development Solution, Gaithersburg, MD, USA), with Pirana 2.9.4 as an interface for NONMEM and Xpose.

The model building process was performed in a stepwise manner.[14] One-, 2- and 3-compartment models were fitted to the log-transformed data. The PPK of vancomycin was characterized in terms of clearance (CL) and volume of distribution (V), and IIV on these parameters was estimated. To account for the differing body weights of neonates and their impact on PK parameters, allometric relationships were examined.[15] Birth weight was standardized to a reference weight of 70 kg for the purpose of comparing parameter estimates with prior published studies. Recognizing the ongoing organ maturation in neonates, maturation models were assessed to gauge the effect of maturation on PK parameter estimates.[16] Residual variability was tested using additive and proportional error models or both. The selection of models was based on goodness-of-fit plots and a significant reduction in objective function value (OFV) of ≥3.8 points, corresponding to a *P*-value of <.05 based on the likelihood ratio test with 1 degree of freedom.[17]

Covariates with potential impact on vancomycin CL were predetermined based on their biological plausibility and existing literature. The associations of these covariates with the PK parameters were tested through a univariate analysis using linear, power or exponential functions. A reduction in OFV by ≥3.8 points was deemed statistically significant (with a *P*-value of <.05). Subsequently, a multivariate analysis was conducted, including all statistically significant covariates from the univariate analyses, using a forward addition procedure. A more stringent reduction in OFV of ≥10.83 (with a *P*-value of <.001) was applied in this phase.

The final model underwent internal validation through prediction-corrected visual predictive checks (pcVPC), and its robustness was evaluated using a bootstrap analysis (both with $n = 1000$ simulations).[14] The model evaluation analyses were performed using Perl-speaks-NONMEM version 3.5.3 software (PsN, Uppsala, Sweden). GraphPad Prism version 9.5.1. for Windows, GraphPad Software, San Diego, CA, USA, www.graphpad.com, was used for visualization of the data.

2.4 | Comparison of vancomycin CL to previously published PPK models

Given that the area under the curve/the minimal inhibitory concentration (AUC_{0-24}/MIC) ratio at present is the PK/PD target for vancomycin, vancomycin CL is the main PK parameter of interest.[3] Since TH has been the standard of care for a considerable duration without available vancomycin PK data predating this period, conducting a randomized controlled trial to investigate differences is ethically and clinically unfeasible This makes a direct comparison in vancomycin CL

between neonates with perinatal asphyxia treated with or without TH unattainable.[8] Additionally, as vancomycin is not a first-line treatment option for early- or late onset sepsis in the Netherlands, a substantial body of real-world PK data was not accessible to us. Therefore, the observed vancomycin CL in term neonates with perinatal asphyxia treated with TH was compared to CL literature values obtained from other neonatal PPK studies.[6,18–20] The collection of vancomycin PPK models was sourced from Hughes et al., as their recent study encompassed an assessment and comparison of frequently employed neonatal vancomycin PPK models for MIPD in clinical settings internationally.[2] Values for vancomycin CL from the individual studies were derived from the final PPK models, utilizing comparable weight, GA, PMA, PNA and SCr values from neonates included in our study. PPK models based on data exclusively from preterm neonates were excluded from this comparison.

2.5 | Simulations to evaluate current and new dosing regimens

Using Monte Carlo simulations ($n = 5000$) with the empirical Bayesian estimates from the final PPK model, existing dosing guidelines (summary of product characteristics, Lexicomp, Dutch paediatric formulary, Neofax Hi-Dose regimens) were evaluated for our patient population.[12,20–23] If these guidelines resulted in suboptimal target attainment, alternative vancomycin dosing regimens were evaluated. A minimum of 90% of simulated neonates with a vancomycin AUC_{0-24}/MIC ratio of 400–600 mg*h/L was used as a target.[3] Insufficient and excessive exposure were defined as an AUC_{0-24}/MIC ratio of <400 and >600 mg*h/L, respectively. The target was based on the assumption of a MIC of 1 mg/L for methicillin-resistant *S. aureus* as susceptibility of the cultured microorganisms was unknown.[3,24] Given that MIPD of vancomycin is usually feasible to perform in clinical practice within the first 2 days of vancomycin treatment, particular emphasis was placed on these initial 48 h.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019a,b).[25]

3 | RESULTS

Out of the 189 included neonates in the PharmaCool study, 16 neonates received vancomycin (8.5%). A total of 112 vancomycin plasma samples were available for analysis, of which 24 samples (21%) were acquired during the hypothermic phase, 6 samples (5%) in the rewarming phase and 82 samples (73%) in the normothermic phase. Patient characteristics are presented in Table 1.

TABLE 1 Patient characteristics and samples drawn.

Characteristic	Vancomycin population $n = 16$[a]
Male, *n* (%)	8 (50.0%)
Birth weight, g (range)	3495 (2295–4720)
GA, weeks (range)[b]	41 (38–42)
PNA, days (range)[c]	4.4 (2.5–5.5)
PMA, days (range)[c]	287.1 (266.0–298.8)
Thompson score (range)[b,f]	10 (7–15)
SCr, μmol/L (range)[d]	49 (15–106)
Urine output, mL/kg/h (range)[d]	2.5 (0.1–8.5)
ASAT (U/L)[d]	67 (23–1127)
ALAT (U/L)[d]	40 (10–498)
MOF, *n* (%)[d,e]	13 (81%)
Renal involvement	4 (31%)
Hepatic involvement	6 (46%)
Both	3 (23%)
Cardiovascular medication, *n* (%)[d]	9 (69%)
Duration of vancomycin treatment, days (range)	2 (0.5–3.5)
Start of vancomycin treatment, study days (range)	4 (2.5–5.5)
Vancomycin dose, mg/kg/day (range)[g]	29.3 (19.9–31.3)
Total number of samples	
During study period	112
During hypothermic phase	24
During rewarming	6
During normothermic phase	82

Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; GA, gestational age; MOF, multiorgan failure; PMA, postmenstrual age; PNA, postnatal age; SCr, serum creatinine.
[a]Baseline characteristics are depicted by median and range for continuous variables and percentages for categorical variables.
[b]Measured at admittance.
[c]Measured at end of study period.
[d]Measured throughout of study period.
[e]Defined as presence of renal or liver failure per criteria outlined by Shah et al.[9]
[f]Thompson score: no unit.
[g]No loading dose was administered.

Vancomycin PPK was best described with a 1-compartment model. The model was parameterized in terms of CL and V. The IIV could be estimated for CL. The allometric exponents describing the impact of body weight on CL and V should not be estimated because of the small dispersion of size.[26] Hence, allometric exponents were set to established literature values of 1 for V and 0.75 for CL.[15] The inclusion of a sigmoidal maturation function to CL in order to account for the further effect of age on kidney maturation after birth did not result in an improvement of our model, probably due to a narrow range in PMA. Given the absence of analogous PK models utilizing maturation functions in neonatal populations with perinatal asphyxia,

we were unable to set the Hill coefficient and time to 50% maturation to literature-derived values. An additive error model best described residual variability. No statistically significant correlations were found between the tested covariates (including PNA and body temperature) and vancomycin CL and V ($P > .05$). The final parameters are shown in Table 2. The model-based final parameter estimates were similar to the bootstrap values and all fell within the 95% confidence intervals of the bootstrap values, indicating stability of the model. As shown by the goodness-of-fit plots (Figure 1) and the pcVPC (Figure 2), the final model described the observed data adequately.

TABLE 2 Parameter estimates of the vancomycin population pharmacokinetic model.

	Final model[a]		Bootstrap[b]	
	Estimate	RSE, % (Shr.)	Estimate	95% CI
CL (L/h/70 kg)	1.63	4	1.63	1.47–1.89
V (L/70 kg)	38.8	7	38.5	35.7–42.7
Additive error (mg/L)	0.238	11	0.237	0.177–0.285
IIV on CL (CV%)	27.7	19 (5)	26.4	13.7–36.8

Note: Final model: $TVCL = 1.63*(WT/70000)^{0.75}$; $TV\ V = 38.8*(WT/70000)^{1}$.
Abbreviations: CI, confidence interval; CL, clearance; CV, coefficient of variation; IIV, interindividual variability; V, volume of distribution; WT, birth weight (g).
[a]As no covariates are retained in the final model: structural model equals final model.
[b]98.9% of runs successful.

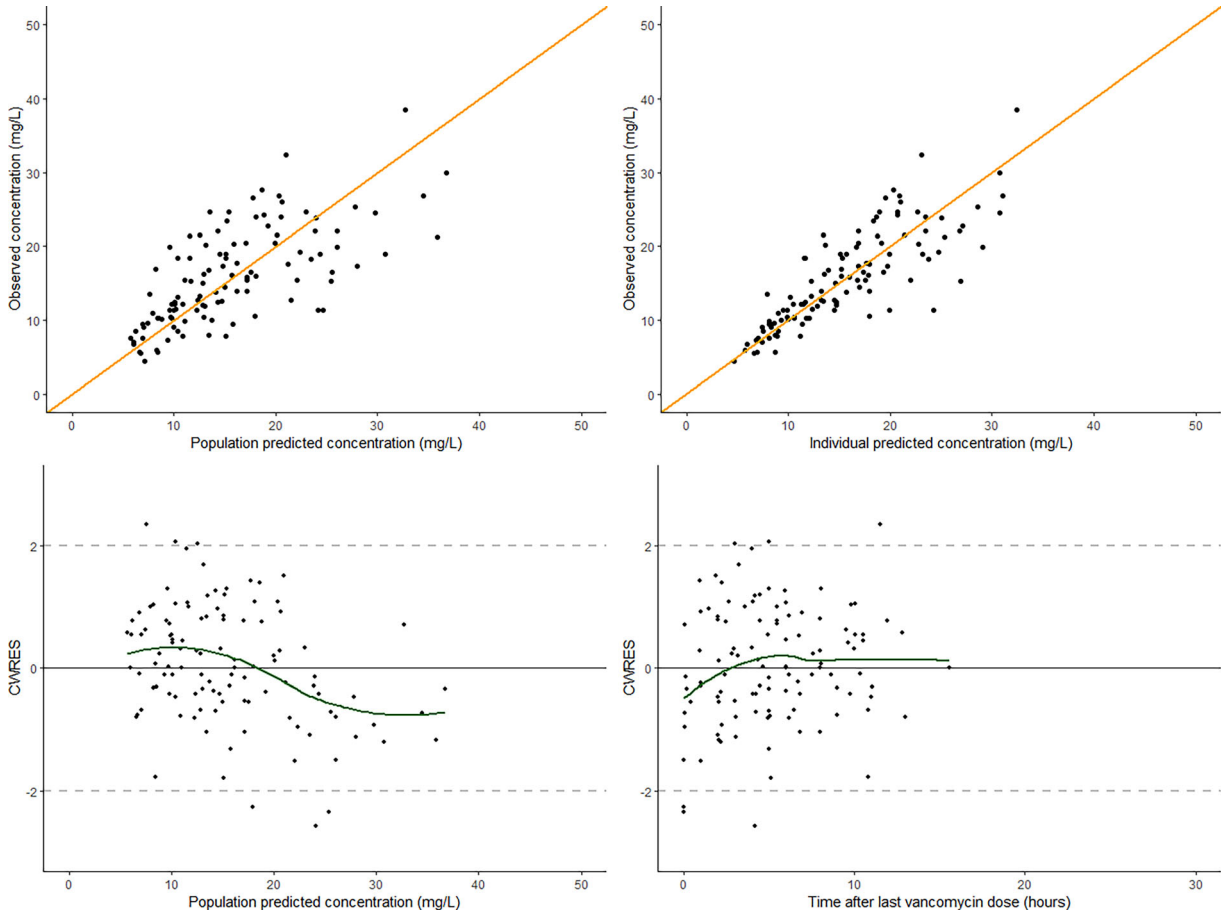

FIGURE 1 Model evaluation of vancomycin. Basic goodness-of-fit plots of the final population pharmacokinetic model. The orange line represents the line of unity and the green line represents the correlation of the observations and predictions. CRWES, conditional weighted residuals [Correction added on 24 April 2024, after first online publication: Figure 1 has been updated in this version.].

Vancomycin PPK parameters found in other neonatal populations were compared to the PK values from the final model in Table 3. Term neonates of 3.5 kg with perinatal asphyxia treated with TH exhibit a lower CL and similar V compared to literature values of term neonates without perinatal asphyxia and TH treatment (CL: 0.17 L/h *vs.* 0.20–0.32 L/h).

In Figure 3, the percentages of simulated patients with insufficient, adequate and excessive vancomycin exposure are shown after 24 and 48 h of vancomycin treatment based on 3 commonly used and 4 newly developed dosing regimens. The dosing regimen from the Dutch paediatric formulary led to appropriate exposure in 72% of simulated neonates after 24 h, but this percentage dropped to 40% after 48 h of vancomycin treatment, with 56% experiencing excessive exposure.[12] Dosing regimens as advised in the summary of product characteristics, or suggested by Lexicomp and Neofax Hi-Dose, resulted in excessive exposure within 24 h of vancomycin treatment (68% and 93%, respectively).[21–23] None of the simulated dosing regimens reached a target attainment of ≥90% due to the considerable IIV. A vancomycin loading dose of 10 mg/kg, followed by 24 mg/kg/day in 4 doses, resulted in the highest percentage of appropriate exposure, both at the initiation and after 48 h of vancomycin treatment.

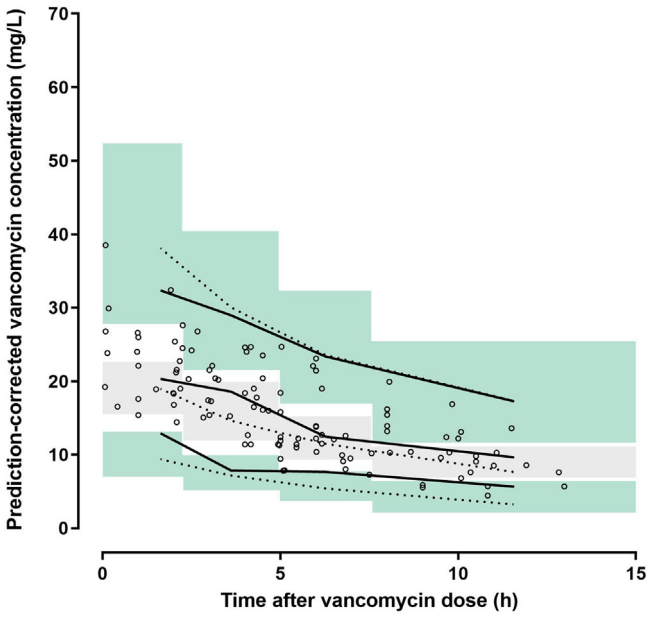

FIGURE 2 Prediction-corrected visual predictive check from the final population pharmacokinetic model. The open circles represent the observed vancomycin concentrations. The black solid lines are the observed median and the 5th and 95th percentiles. The black dotted lines represent the predicted percentiles. The light grey area indicates the 95% confidence interval of the model-predicted median and the green area indicates the model-predicted 5th and 95th percentiles. The model generally captured the data effectively since the observed medians of the 5th, 50th and 95th percentiles lay within the 95% confidence interval of the model-predicted percentiles.

4 | DISCUSSION

This is the first prospectively conducted study investigating the PPK of vancomycin in term neonates with perinatal asphyxia treated with TH. Our findings indicate a lower vancomycin CL in comparison to term neonates without perinatal asphyxia treated with TH, causing conventional dosing regimens to result in vancomycin overexposure. We suggest using an initial dosing regimen of a 10-mg/kg loading dose followed by 24 mg/kg/day in 4 doses.

The observed lower vancomycin CL in these neonates with perinatal asphyxia is not unexpected: the cardiovascular reaction to the asphyxia prompts organ-specific vasoconstriction. This subsequently leads to redistribution of perfusion and oxygen supply from the non-essential organs to the heart and brain, while the kidneys operate within a low-perfusion context.[27] This compromised oxygen delivery to the kidneys may result in acute kidney injury due to the limited anaerobic respiration capacity of renal parenchymal cells and their heightened susceptibility to reperfusion injury.[28] TH may further reduce end-organ perfusion by decreasing cardiac output.[29] In general, neonates with perinatal asphyxia treated with TH show notably elevated median SCr levels in the first week of life, with a greater incidence of acute kidney injury when compared to healthy controls without asphyxia, indicating impaired renal function.[4,27,30–32] In our study, 81% of the neonates who received vancomycin had MOF, indeed reflecting a substantial disease burden. However, a recent meta-analysis indicates a potential reno-protective effect of whole-body TH treatment in neonates with perinatal asphyxia. The authors suggest that this reno-protective effect might be attributed to similar underlying pathogenic mechanisms as TH's neuroprotective effect. These mechanisms involve a reduced metabolic rate leading to decreased free radical release and the suppression of apoptotic processes through the inhibition of caspase enzymes.[33] Other possible explanations for the lower vancomycin CL relative to literature values could involve a delay in renal maturation due to cooling or in recovery of organ function after the asphyxia.[10,27,29,33,34]

As vancomycin was generally used as a second-line antimicrobial agent in this population (mostly after the third day of life) samples were predominantly collected during the rewarming and normothermic phase. We were therefore not able to describe the vancomycin CL during the hypothermic phase separately. For this reason, a proper comparison of CL between the different phases could not be made, unlike with other renally cleared antibiotics.[10,11,35,36] These studies observed a higher CL independent of PNA during the normothermic phase in contrast to the preceding hypothermic and rewarming phases. Nevertheless, we still observed relatively lower vancomycin CL in neonates with perinatal asphyxia when compared to literature values of vancomycin CL in neonates without perinatal asphyxia or TH. As vancomycin is generally not initiated as empirical therapy for early-onset sepsis, it is rarely administered in the first 3 days of life. Therefore, precise dosing of vancomycin during the rewarming and normothermic phases holds paramount clinical relevance. However, it should be taken into consideration that vancomycin CL might be even lower when exclusively used during the hypothermic phase.

TABLE 3 Comparison of neonatal vancomycin population pharmacokinetic models.

	PharmaCool ($n = 16$)[d]	Capparelli ($n = 374$)[19]	Dao ($n = 405$)[6]	Frymoyer ($n = 249$)[18]	Jacqz-Aigrain ($n = 1463$)[20]
GA, weeks[a]	41 (39–42)	33.5 (28–40)	29 (24–42)	34 (22–42)	30.0 (22.3–42.1)
PNA, days[a]	4,9 (4.4–5.3)	27 (15–74)	12.3 (0–146)	19 (0–173)	11 (1–90)
PMA, weeks[a]	41 (39–43)	NA	32 (25–61)	39 (24–54)	32 (23–52)
Weight, kg[a]	3.5 (2.3–4.7)	2 (1.0–3.6)	1.1 (0.5–5.7)	2.9 (0.4–4.4)	1.4 (0.4–11.4)
Term[b], *n*	16	135	74	NA	NA
Compartments	1	2	1	1	2
Model for CL (L/h)	$\theta1 \cdot (WT / 70)^{0.75}$	$0.006 + WT \cdot (\theta1 / CR + 0.046355 \cdot AGE + 0.0123)$	$\theta1 \cdot (WT / 1)^{\theta2} \cdot (0{,}61 / CR)^{\theta3} \cdot (PMA^{HILL} / (PMA^{HILL} + T50^{HILL}))$	$\theta1 \cdot (WT / 2.9)^{0.75} \cdot (1 / CR)^{\theta2} \cdot (1 / (1 + (PMA / T50)^{-HILL}))$	$\theta1 \cdot (WT / 1.35)^{\theta2} \cdot (PMA / 32)^{\theta3} \cdot (0.61086 / CR)^{\theta4}$
Model for V (L)	$\theta2 \cdot (WT / 70)^{1}$	$\Theta2 \cdot WT + 0.010$	$\Theta4 \cdot WT$	$\Theta3 \cdot (WT / 2.9)^{1}$	$\Theta5 \cdot (WT / 1.35)^{\theta6}$
Model for Q (L/h)		$\Theta3 \cdot WT$			$\Theta9 \cdot (WT / 1.35)$
Model for V2 (L)		$\Theta4 \cdot V$			$\Theta7 \cdot (WT / 1.35)^{\theta8}$
Final PK parameters	$\theta1 = 1.63$ $\theta2 = 38.8$	$\theta1 = 0.028$ $\theta2 = 0.793$ $\theta3 = 0.0334$ $\theta4 = 0.666$	$\theta1 = 0.268$ $\theta2 = 0.438$ $\theta3 = 0.483$ $\theta4 = 0.629$ $HILL = 3.57$ $T50 = 46$	$\theta1 = 0.345$ $\theta2 = 0.267$ $\theta3 = 1.75$ $HILL = 4.53$ $T50 = 34.8$	$\theta1 = 0.068$ $\theta2 = 0.863$ $\theta3 = 0.544$ $\theta4 = 0.66$ $\theta5 = 0.728$ $\theta6 = 1.13$ $\theta7 = 0.358$ $\theta8 = 1.15$ $\theta9 = 0.0301$
CL (L/h)[c]	0.172	0.269	0.199	0.317	0.213
V (L)[c]	1.9	2.8	2.2	2.1	2.1

Abbreviations: AGE, age in years; CL, clearance; CR, serum creatinine (mg/dL); GA, gestational age; HILL: Hill coefficient; NA, not available; PK, pharmacokinetics; PNA, postnatal age; PMA, postmenstrual age; Q, intercompartmental clearance; SCr, serum creatinine (mg/dL); V, volume of distribution central compartment; V2, volume of distribution peripheral compartment; WT, weight.

[a]Around vancomycin administration, depicted as median and range, except for the Capparelli model (median and interquartile range).

[b]Term: GA > 36 weeks.

[c]CL and V modified for a typical neonate of 3.5 kg with GA 39, PNA 5, PMA 39.7, SCr 40 μmol/L (=0.45 mg/dL), caution should be exercised in interpreting the data and conclusions, as the proportion of term neonates was somewhat underrepresented or unknown in the studies used for comparison.

[d]Only study including neonates with perinatal asphyxia treated with therapeutic hypothermia.

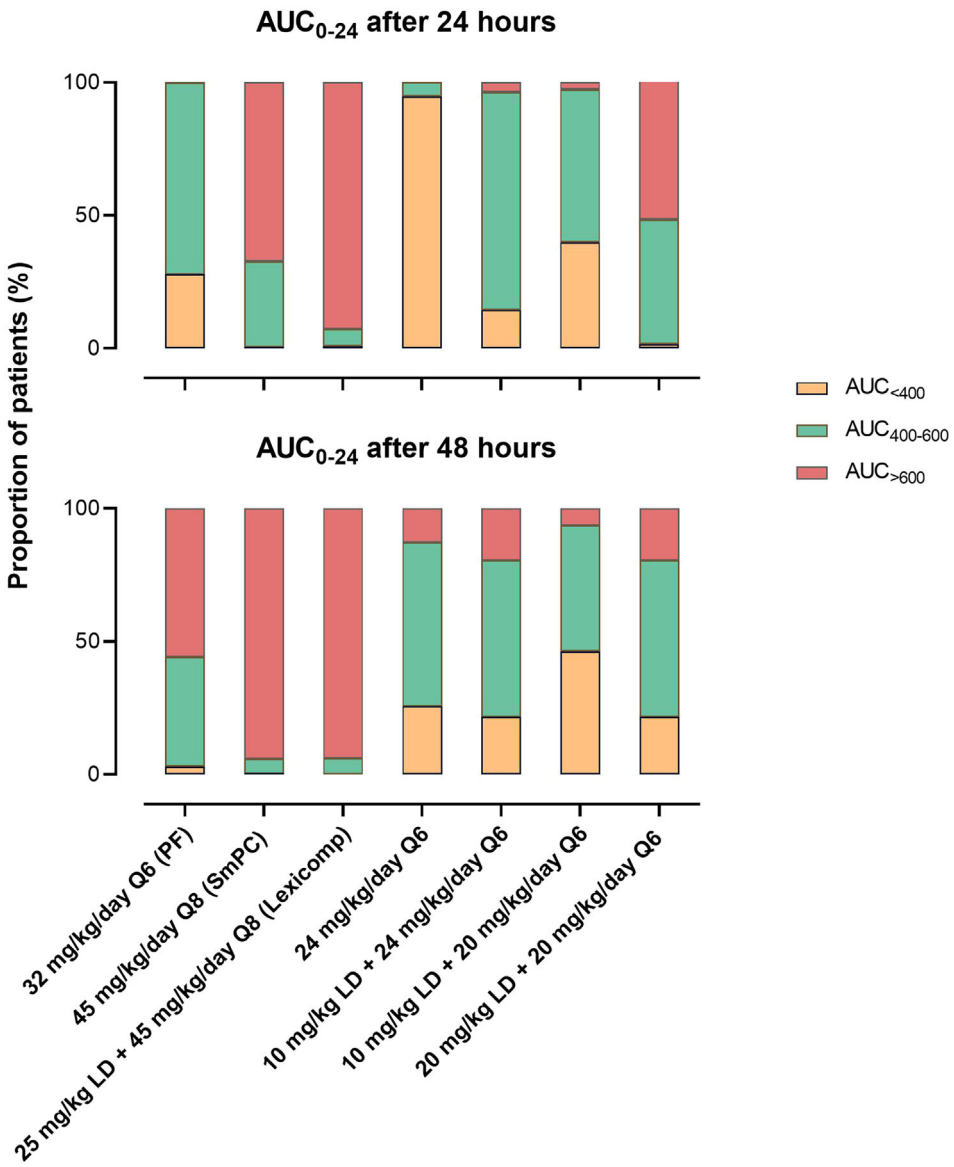

FIGURE 3 Percentage of simulated patients with an adequate vancomycin exposure (AUC 400–600 mg*h/L), insufficient (AUC < 400 mg*h/L) or excessive (AUC > 600 mg*h/L) for 3 commonly used (Dutch paediatric formulary, summary of product characteristics, Lexicomp) and 4 newly developed dosing regimens. AUC, area under the curve; LD, loading dose; PF, Dutch paediatric formulary; Q, dosing interval.

Unlike other neonatal vancomycin PPK studies, we were not able to detect an influence of SCr or age (generally PMA on renal maturation) on vancomycin CL.[6,18–20,37] The distribution of these covariates in our relatively small study population was limited as only (near) term neonates, most of whom experienced organ dysfunction as a consequence of the perinatal asphyxia, were included during the first 6 days of life. This poses a challenge in detecting their potential impact on vancomycin CL. Unlike our study, these other studies incorporated neonates older than 1 week, as well as those who were premature. Additionally, the utility of SCr levels in the early days of life as a reliable parameter is compromised by their reflection of maternal SCr.[38] While there is still no consensus on the optimal marker for renal function in neonates during their initial days, some neonatal PPK studies suggest that SCr can effectively predict vancomycin levels.[2]

Interestingly, adhering to the vancomycin initial dose as recommended by most of the above-mentioned studies (i.e. loading dose of 25 mg/kg, followed by 45 mg/kg/day in 3 doses), brings a large majority of neonates with perinatal asphyxia treated with TH above target within 24 h of treatment.[6,18,20,23] It is important to highlight that the absence of a definitive consensus on vancomycin dosing in neonates has resulted in a heterogeneous empirical dosing approach in clinical practice worldwide.[39] As more research emerges to explore the optimal vancomycin dosing strategy for neonates in general, there is a growing trend to disfavour regimens with low doses due to their inadequate exposure outcomes, and to adopt regimens with high loading and maintenance doses.[6,23] PPK studies that have provided the basis for the latter dosing regimens have also demonstrated their suitability for MIPD in neonates.[2] Nonetheless, it is crucial to exercise caution when applying these findings to neonates with perinatal asphyxia treated with TH. Adoption of these regimens with higher doses could immediately lead to excessive exposure, necessitating a more conservative dosing approach such as our proposed regimen. However, MIPD should also be employed in this population (preferably within 24 h of treatment), acknowledging the need for meticulous adjustment in vancomycin dosing given its high IIV.[40]

Our study has some limitations. First, we were not able to explain IIV by inclusion of covariates (such as PNA and body temperature) in our PK model. Second, the administration of vancomycin was limited to a relatively small number of patients in our study, which should be taken into consideration when generalizing our findings. Our PPK model should be prospectively validated to confirm our proposed model-derived dosing regimen and to assess the performance of our PPK model in a MIPD context in clinical care. Lastly, we were unable to compare the observed vancomycin CL in neonates treated with TH for perinatal asphyxia to those not treated with TH, due to the absence of available data. As an alternative, we opted to compare the found CL value with literature values of neonates without perinatal asphyxia or TH. This approach provides perspective into the CL observed in our specific neonatal population relative to other neonatal populations, as a direct comparison was not feasible. Caution should be exercised in interpreting the data and conclusions, as the proportion of term neonates was somewhat underrepresented or unknown in the studies used for comparison. Nevertheless, our study is, to the best of our knowledge, the first to provide insight into the vancomycin CL in neonates with perinatal asphyxia treated with TH. It underlines the caution required in clinical decision-making when employing higher vancomycin dosing regimens in this specific neonatal population.

5 | CONCLUSION

Term neonates with perinatal asphyxia treated with TH have a lower vancomycin CL in comparison to neonates without perinatal asphyxia treated with TH. Internationally recognized dosing regimens often result in excessive vancomycin exposure in these neonates already in the first 24 h of treatment. We propose an initial dosing regimen for the first 48 h of treatment with PK/PD target attainment in case vancomycin is used as a second-line antibiotic, consisting of a 10-mg/kg loading dose and 24 mg/kg/day in 4 doses followed by MIPD.

AUTHOR CONTRIBUTIONS

All authors attest that they meet the current ICMJE criteria for authorship.

ACKNOWLEDGEMENTS

Collaborators of the PharmaCool study group include Mieke J. Brouwer, Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; Marcel P. van den Broek, and Carin M.A. Rademaker, Pharmacy Department, University Medical Center Utrecht, Utrecht, The Netherlands; Djien Liem and Katerina Steiner, Department of Neonatology, Radboud University Medical Center, Nijmegen, The Netherlands; Sinno H.P. Simons and Annelies A. Bos, Department of Pediatrics, Division of Neonatology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands; S.M. Mulder-de Tollenaer and L.J.M. Groot Jebbink-Akkerman, Department of Neonatology, Isala Clinics, Zwolle, The Netherlands; and Michel Sonnaert and Fleur Anne Camfferman, Department of Neonatology, Vrije Universiteit Brussel, Brussels, Belgium.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data are available upon reasonable request.

ORCID

Marlotte A. A. van der Veer https://orcid.org/0000-0002-2600-1381

Linda G. W. Franken https://orcid.org/0000-0001-6436-9825

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How to cite this article: van der Veer MAA, de Haan TR, Franken LGW, et al. Population pharmacokinetics of vancomycin in term neonates with perinatal asphyxia treated with therapeutic hypothermia. *Br J Clin Pharmacol*. 2024;90(6):1418-1427. doi:10.1111/bcp.16026