Model-Informed Vancomycin Dosing Optimization to Address Delayed Renal Maturation in Infants and Young Children with Critical Congenital Heart Disease

Yuko Shimamoto[1,2], Keizo Fukushima[3], Tomoyuki Mizuno[3,4], Hajime Ichikawa[5], Kenichi Kurosaki[6], Shinichiro Maeda[7] and Masahiro Okuda[2,*]

Ensuring safe and effective drug therapy in infants and young children often requires accounting for growth and organ development; however, data on organ function maturation are scarce for special populations, such as infants with congenital diseases. Children with critical congenital heart disease (CCHD) often require multiple staged surgeries depending on their age and disease severity. Vancomycin (VCM) is used to treat postoperative infections; however, the standard pediatric dose (60–80 mg/kg/day) frequently results in overexposure in children with CCHD. In this study, we characterized the maturation of VCM clearance in pediatric patients with CCHD and determined the appropriate dosing regimen using population pharmacokinetic (PK) modeling and simulations. We analyzed 1,254 VCM serum concentrations from 152 postoperative patients (3 days–13 years old) for population PK analysis. The PK model was developed using a two-compartment model with allometrically scaled body weight, estimated glomerular filtration rate (eGFR), and postmenstrual age as covariates. The observed clearance in patients aged ≤ 1 year and 1–2 years was 33% and 40% lower compared with that of non-CCHD patients, respectively, indicating delayed renal maturation in patients with CCHD. Simulation analyses suggested VCM doses of 25 mg/kg/day (age ≤ 3 months, eGFR 40 mL/min/1.73 m^2) and 35 mg/kg/day (3 months < age ≤ 3 years, eGFR 60 mL/min/1.73 m^2). In conclusion, this study revealed delayed renal maturation in children with CCHD, could be due to cyanosis and low cardiac output. Model-informed simulations identified the lower VCM doses for children with CCHD compared with standard pediatric guidelines.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The maturation of kidney function can significantly influence optimal dosing regimens for renally eliminated drugs in young children. However, maturation data are often lacking for young children with rare disease conditions, such as critical congenital heart disease (CCHD). Children with CCHD require multiple staged surgeries and antibiotic therapy is crucial after surgery, nonetheless, there are no specific vancomycin (VCM) dose guidelines for this population.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ This study characterized the unique maturation of VCM clearance in pediatric patients with CCHD to determine appropriate dosing regimens for this special population.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We developed a pediatric CCHD-specific VCM population pharmacokinetic model and demonstrated that VCM clearance is consistently lower in patients with CCHD aged 0–3 years compared with data generated using a previously published model for non-CCHD patients. Age- and renal function-appropriate VCM dosing regimens were determined based on simulations, which address the observed delayed renal maturation in children with CCHD.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This study highlights the importance of understanding the varying maturation of organ function to provide precision dosing in young children with special disease conditions. The developed dosing regimens may provide more effective and safer antibiotic therapy for children with CCHD. In addition, the observed delayed maturation of VCM clearance may inform optimal dosing strategies for other renally eliminated drugs in children with CCHD and provide valuable insights for studies on the maturation of kidney function.

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[1]Department of Pharmacy, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan; [2]Department of Hospital Pharmacy, Graduate School of Medicine, Osaka University, Suita, Osaka, Japan; [3]Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [4]Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, Ohio, USA; [5]Department of Pediatric Cardiovascular Surgery, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan; [6]Department of Pediatric Cardiology, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan; [7]Center for Advanced Education and Research in Pharmaceutical Sciences Clinical Pharmacology and Therapeutics, Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka, Japan. *Correspondence: Masahiro Okuda (okudam@hp-drug.med.osaka-u.ac.jp)

Ensuring safe and effective drug therapy for infants and young children often requires accounting for growth in body size and the development of organ function, as rapid and dynamic physiological changes can affect drug disposition, exposure, and response. To date, several studies have characterized renal function maturation to provide optimal dosing strategies for renally eliminated drugs in infants and young children.[1–5] These maturation profiles have been successfully incorporated into population pharmacokinetic (PK) and pharmacodynamic models for various drugs to identify age-appropriate dosing regimens through model-informed precision dosing.[6–10] However, these studies were primarily focused on relatively healthy subjects. Characterizing renal maturation in special populations, such as infants with congenital diseases, remains an important unmet need for providing precision therapeutic strategies for these individuals.

Congenital heart disease is the most common congenital anomaly, which affects ~1% of liveborn children.[11] Critical congenital heart disease (CCHD) comprises ~20–25% of congenital heart disease and can lead to significant morbidity and mortality, requiring surgery or intervention.[11] Neonates with CCHD have a higher risk of low birth weight, premature birth, and low body weight at gestational age.[12,13] Although the etiology of CCHD in children is poorly understood, abnormal circulatory physiology in fetuses with CCHD may contribute to poor growth and preterm labor.[14,15]

Children with CCHD often require multiple staged surgeries depending on the disease condition and age. After cardiac surgery, these patients are at high risk for acute kidney injury resulting from various factors, such as low cardiac output syndrome, venous congestion, and reduced renal blood flow.[16] Consequently, appropriate antibiotic therapy is required to prevent severe postoperative infections in children following surgery in the intensive care unit. The pediatric vancomycin (VCM) dosage recommended by the Infectious Diseases Society of America (IDSA) guidelines is 60–80 mg/kg/day for all degrees of renal function when targeting an area under the curve/minimum inhibitory concentration (AUC/MIC) ratio of 400–600[17]; however, this recommended dosage often results in overexposure and requires dose reduction in infants and young children with CCHD at our institution. Currently, there are no specific dosing guidelines for this population.

In this study, we characterized the maturation of VCM clearance in infants and young children with CCHD and determined an age-appropriate dosing regimen for this special population using population PK modeling and simulations.

MATERIALS AND METHODS

Study design and patient selection

This was an observational PK study collecting data from electronic medical records (EMRs) and using an opportunistic sampling strategy from patients who provided informed consent. Patient inclusion criteria were: aged younger than 18 years old, and postoperative patients with CCHD who underwent VCM treatment in the intensive care unit. All patients on renal replacement therapy at the time of VCM treatment were excluded. The study protocol was approved by the Institutional Research Ethics Board at the National Cerebral and Cardiovascular Center, Osaka, Japan (R22018).

Data collection

Clinical and laboratory data were retrieved from EMRs and included demographics, physical parameters, VCM dosage, and concomitant treatments. The VCM trough concentrations measured for clinical routine therapeutic drug monitoring (TDM) were obtained from the EMR. Furthermore, residual samples obtained for laboratory tests or gas analysis were collected with no intervention and observationally for VCM measurement to enrich the PK data from patients who provided informed consent ($n = 54$, 247 samples). The patients' demographics were not significantly different between these two cohorts (**Table S1**). The estimated glomerular filtration rate (eGFR) was calculated using the revised Schwartz equation, as described previously.[3]

$$\text{eGFR}\left(\text{mL}/\text{min}/1.73\ \text{m}^2\right) = k \times \frac{\text{height}\,(\text{cm})}{\text{serum creatinine}\left(\text{mg}/\text{dL}\right)}$$

where the derived k values in the equation were 0.244 for low birth weight infants (< 1 year, body weight (BW) < 2.5 kg), 0.277 for non-low birth weight infants (< 1 year, BW ≥ 2.5 kg), and 0.296 for children (1–12 years).

Postmenstrual age (PMA) was calculated for all patients as follows:

$$\text{PMA (week)} = \text{Gestational age (week)} + \text{postnatal age (week)}$$

Vancomycin serum concentration measurement

VCM concentrations for clinical routine TDM and residual samples were measured using a Cobas 6000 (Roche Diagnostics, Tokyo, Japan) and liquid chromatography–tandem mass spectrometry (LC–MS/MS; Shimadzu Corporation, Kyoto, Japan), respectively (see details in **Supplementary Material**). A mean proportional difference between VCM concentrations measured by Cobas 6000 and LC–MS/MS was within 10%.

Population PK modeling

Population PK modeling and simulation were performed using a nonlinear mixed effect modeling software, Phoenix NLME 8.4 (Certara, Princeton, NJ). To account for the effect of body size differences, the allometrically scaled body weight was applied to volumes of distribution (V) and clearance (CL) in the base model with power coefficients of 1.0 and 0.75, respectively[18–20]:

$$V_i = V_{\text{pop}} \times \left(\frac{\text{BW}}{70}\right)^{1.0}$$

$$\text{CL}_i = \text{CL}_{\text{pop}} \times \left(\frac{\text{BW}}{70}\right)^{0.75}$$

where V_i and CL_i are individual V and CL, and V_{pop} and CL_{pop} are the population mean of V and CL, respectively; BW represents individual body weight.

Covariate analysis and model development and validation

Patient demographics and laboratory parameters were evaluated as candidate covariates on PK parameters using an exponential model. GFR increases rapidly during the first days of life and then steadily increases until adult values are reached at 8–12 months of age.[21,22] To explain the developmental change, the maturation function (F_{mat}) described by PMA was evaluated as a covariate on CL as follows:

$$F_{mat} = \frac{PMA^{Hill}}{TM_{50}{}^{Hill} + PMA^{Hill}}$$

where TM_{50} is the PMA at which 50% of the maturation effect is reached and Hill is a slope of the maturation profile. Univariate analysis was conducted by individually incorporating each candidate covariate into the base model (see details in the **Supplementary Material**).

Comparison of vancomycin clearance maturation between CCHD and non-CCHD pediatric patients

To evaluate the differences in VCM CL between pediatric patients with and without CCHD, two published VCM population PK models for non-CCHD pediatric patients, Colin and Kloprogge models, were used for simulation.[23,24] The Colin model was developed using pooled data from 14 pediatric and adult studies with an age range of 1 day to 101 years old. The Kloprogge model was developed with data from 616 pediatric patients with an age range of 1 day to 21 years old. Both models exhibited similar PK parameters and covariate structures, including a 2-compartment model structure with allometric body weight scaling, F_{mat}, and renal function described by serum creatinine. The simulated CLs in the non-CCHD pediatric patients corresponding to patients in the present study were generated using the Colin and Kloprogge models with individual covariate values observed in this study (BW, PMA, and serum creatinine). The simulated non-CCHD CLs were compared with observed CL in pediatric patients with CCHD. To compare the maturation profiles of the three models (i.e., Colin, Kloprogge, and our final models), relative CL to the value at a PMA of 40 weeks for individuals was calculated based on the following formula:

$$\text{Relative } CL_i = \frac{F_{mat,i} \times e^{\eta CL_i}}{F_{mat,40}}$$

where $F_{mat,i}$ and ηCL_i are individual maturation effect and ηCL value, respectively, and $F_{mat,40}$ is the maturation effect at a PMA of 40 weeks. Similarly, to facilitate a comparison between models, the maturation functions in the final, Colin, and Kloprogge models were normalized to the corresponding values at a PMA of 40 weeks and overlaid on the relative CLs observed in the present study.

Age and renal function appropriate dosing design based on model-informed simulations

To obtain the target attainment rate in the dosing simulation, a realistic virtual CCHD pediatric population was generated based on the age vs. body weight distribution observed in patients with CCHD. The observed age-matched body weight was modeled with a Box-Cox power exponential distribution using generalized additive modeling for location, scale, and shape (GAMLSS) strategy as implemented in the R software package library GAMLSS (version 4.3-8 under R.4.0).[25] The virtual age-matched body weight dataset (e.g., virtual CCHD pediatric population) was generated by the fitted model at 5 patients per 0.01 month up to 36 months (18,000 patients in total). The VCM CL in the virtual CCHD pediatric population was estimated by the developed population PK model at any given eGFR value. The daily steady-state AUC for a given daily VCM dose was then calculated by dividing the daily dose by CL. A target AUC/MIC ratio of 400 and 600 were used for the efficacy and safety target, respectively,[17] and the target attainment rate was calculated at a given eGFR and a given daily VCM dose. An MIC of 1 mg/L was used for the simulation because it is the most frequently reported MIC for methicillin-resistant *Staphylococcus aureus* (MRSA) in the European Committee on Antibacterial Susceptibility Testing (EUCAST) database.[26]

Age stratification was performed based on whether improvement in the target attainment rate in an age group exceeded 5% when dividing into 2 smaller groups. Finally, the daily dose that maximized the target attainment rate for a given eGFR value in each age group was considered the recommended daily dose.

RESULTS

Patient demographics and clinical characteristics

The demographics and clinical characteristics of the patients are summarized in **Table 1**. Of 152 patients enrolled in this study, 136 were younger than 3 years old. Body weight and height in 74% and 64% of all patients, respectively, were less than the fifth percentile in the growth charts of the Centers for Disease Control and Prevention (CDC).[27] The enrolled population included 37%

Table 1 Patient characteristics and vancomycin dosing and concentrations

	Median	IQR	Range
Number of patients, *n*	152		
Gender, n			
Male	74		
Female	78		
Age, year	0.33	0.09–1.31	0.01–13.53
PMA, week	55.2	43.5–107.1	37.9–744.7
BW, kg	4.6	3.1–7.9	1.8–38.7
Height, cm	57.5	48.5–72.3	41.0–153.0
SCr, mg/dL	0.32	0.25–0.39	0.11–1.06
eGFR, mL/min/1.73 m^2	55.2	40.7–71.7	11.7–159.9
EF, %	68	60–77	31–93
POD, day	0	0–6	0–31
CPB (%)	82.2		
CPB time, minutes	206	144–273	40–575
Lowest BT during CPB, °C	27	24–28	13–35
Vancomycin dosing			
Number of dosing, *n*	1790		
Dose amount, mg/kg	13.2	10.5–18.5	2.8–41.0
Dosing interval, hours	12.0	10.5–13.3	2.7–167.9
Infusion time, hours	2	2–2	2–2
Vancomycin concentrations			
Number of observations, *n*	1,254		
Concentration, mg/L	12.0	8.6–17.2	1.7–70.0
Sampling time after dosing, hours	9.6	7.2–10.5	1.2–71.1

BT, body temperature; BW, body weight; CPB, cardiopulmonary bypass; EF, ejection fraction; eGFR, estimated glomerular filtration rate calculated by the revised Schwartz equation[3]; IQR, interquartile range; PMA, postmenstrual age; POD, postoperative day; SCr, serum creatinine.

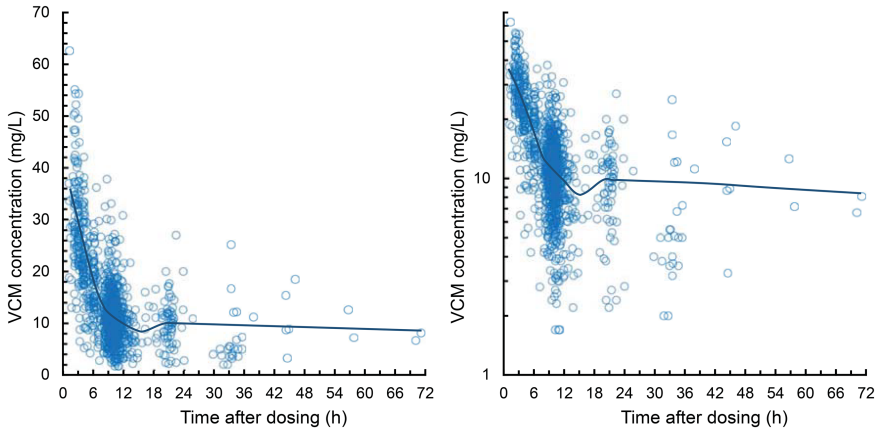

Figure 1 Observed VCM concentration vs. time following administration to pediatric patients with CCHD. CCHD, critical congenital heart disease; VCM, vancomycin.

of patients with single ventricle physiology, who had severe low cardiac output and cyanosis, and 58% with two-ventricle CCHD who had low cardiac output (**Table S2**).

Vancomycin concentrations and population PK model development

A total of 1,254 VCM serum concentrations from 152 patients were collected (**Figure 1**). Most patients received VCM twice a day at a median dose of 13.2 mg/kg (**Table 1**). In addition to the trough concentration, the data included concentrations less than 6 hours after dosing obtained using an opportunistic sampling approach ($n = 251$, 20% of all observations), enabling a description using a 2-compartment model. The results of a univariate analysis revealed statistically significant covariates for CL in the following order: eGFR, serum creatinine (SCr), PMA, ejection fraction (EF), and cardiopulmonary bypass (CPB; **Table S3**). Including eGFR as

Table 2 Final population PK structure and estimates and bootstrap validation (n = 1,000)

	Original data set		Bootstrap replication, n = 1,000			
	Estimate	RSE, %	Median	2.5th	97.5th	Bias, %
Final model structure						
$V1 = \theta_{V1} \times \left(\frac{BW}{70}\right)$						
$CL = \theta_{CL} \times \left(\frac{BW}{70}\right)^{0.75} \times \left(\frac{eGFR}{120}\right)^{\theta_{eGFR}} \times \left(\frac{PMA^{Hill}}{TM_{50}{}^{Hill}+PMA^{Hill}}\right)$						
$V2 = \theta_{V2} \times \left(\frac{BW}{70}\right)$						
$CL2 = \theta_{CL2} \times \left(\frac{BW}{70}\right)^{0.75}$						
Population mean						
θ_{V1}, L	21.6	9.5	21.6	17.9	25.7	0.02
θ_{CL}, L/h	4.88	7.8	4.87	4.15	6.21	0.06
θ_{V2}, L	21.7	8.0	21.8	18.3	25.3	−0.50
θ_{CL2}, L/h	2.95	15.6	2.93	2.14	3.96	0.59
θ_{eGFR}	0.551	7.2	0.545	0.454	0.622	1.05
Hill	1.73	30.1	1.74	0.87	5.84	−0.60
TM_{50}, week	36.9	9.3	38.4	32.4	53.6	−4.21
Interindividual variability						
ω_{CL}, %	22.7	20.9	22.5	17.7	27.5	1.03
ω_{V2}, %	41.5	24.9	43.0	30.3	55.2	−3.56
Residual variability						
Additive, mg/L	0.975	24.5	0.950	0.063	1.482	2.52
Proportional, %	24.1	4.5	23.9	21.6	26.2	0.68

Bias = (estimated value from original data set − median estimated value from bootstrap replications)/estimated value from original data set × 100; BW, body weight (kg); CL, clearance; eGFR, estimated glomerular filtration rate calculated by the revised Schwartz equation[3]; Hill, Hill coefficient; PK, pharmacokinetic; PMA, postmenstrual age (weeks); RSE, relative standard error; TM_{50}, postmenstrual age at which 50% of adult clearance is reached; V, volume of distribution.

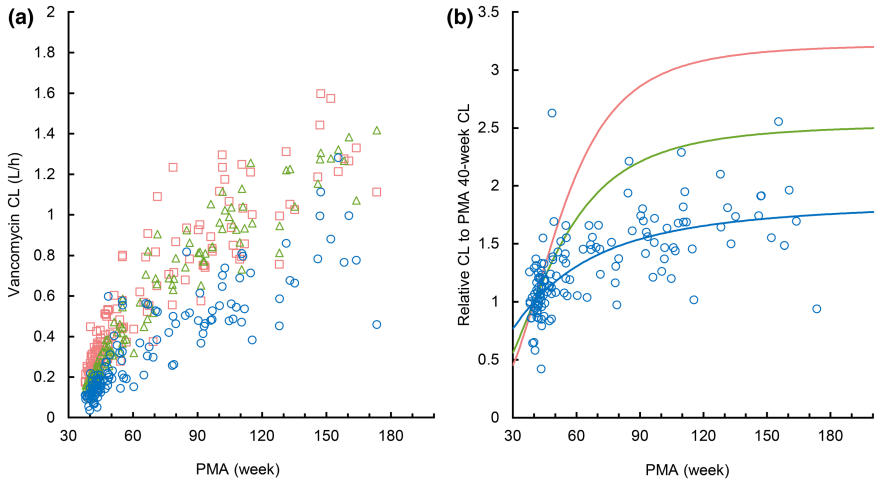

Figure 2 Comparison of VCM CL (**a**) and maturation functions (**b**) observed in pediatric patients with CCHD to predictions in the literature up to 200 weeks. In the left panel, open circles represent observed clearances in this population. Triangles and squares represent predicted clearances by the Colin or Kloprogge model[23,24] using individual values observed in the present study (BW, PMA, and serum creatinine), respectively. In the right panel, open circles represent the observed maturation effects in this study normalized to the clearance value at a PMA of 40 weeks: $(F_{mat,i} \times e^{\eta CL_i}) / F_{mat,40}$. Blue, green, and pink lines represent the maturation curves normalized to the value at a PMA of 40 weeks in this population, the Colin model, and the Kloprogge model, respectively. BW, body weight; CCHD, critical congenital heart disease; VCM, vancomycin; CL, clearance; F_{mat}, maturation function; PMA, postmenstrual age.

a covariate improved the model fit better than SCr (**Table S3**). The inclusion of EF as a covariate on CL also resulted in model improvement by univariate analysis, but not after the inclusion of eGFR due to the collinearity (**Tables S3, S4**). No statistically significant covariates on V were identified. For the stepwise forward inclusion, eGFR and PMA were selected in the full model, whereas eta CL2 and eta V1 were fixed at 0 in the backward elimination (**Table S4**). The goodness-of-fit plots and prediction-corrected visual predictive check (pcVPC) are shown in **Figures S1** and **S2**, respectively. The final model structure and estimates as well as the bootstrap validation results are summarized in **Table 2**. The estimated Hill coefficient (1.73) in the maturation function was 40% lower compared with that reported by Colin *et al.* (2.89), indicating delayed renal maturation.

Comparison of vancomycin clearance maturation between CCHD and non-CCHD pediatric patients

The observed CL in this population and the simulated CL from the Colin and Kloprogge model up to 200 weeks (~ 3 years old) are shown in **Figure 2a**, and pcVPC of VCM CL by 2 models are shown in **Figure S3**. The mean observed CL at age ≤ 1 year (~ 100 weeks) was 33% ± 18 and 47% ± 13 (mean ± standard deviation) lower compared with those simulated by Colin and Kloprogge models, respectively. The observed maturation effects, normalized to the CL value at a PMA of 40 weeks, were well-described by the maturation curve of the final model, most of which were lower compared with those of the Colin and Kloprogge models (**Figure 2b**).

Dosing simulation and target attainment analysis

The body weight of the virtual CCHD pediatric patients generated from this population and the corresponding VCM CL normalized to an eGFR of 120 mL/min/1.73 m^2 are shown in **Figure 3**. The body weight distribution of the virtual patients was in good agreement with the observations in CCHD patients under 36 months of age (**Figure 3a**). The simulated VCM CLs for the virtual CCHD pediatric patients were also consistent with the observations for patients under 36 months old (**Figure 3b**). An example distribution for the daily AUC at steady-state at a VCM dose of 25 mg/kg/day simulated in virtual CCHD pediatric patients with an eGFR of 40 mL/

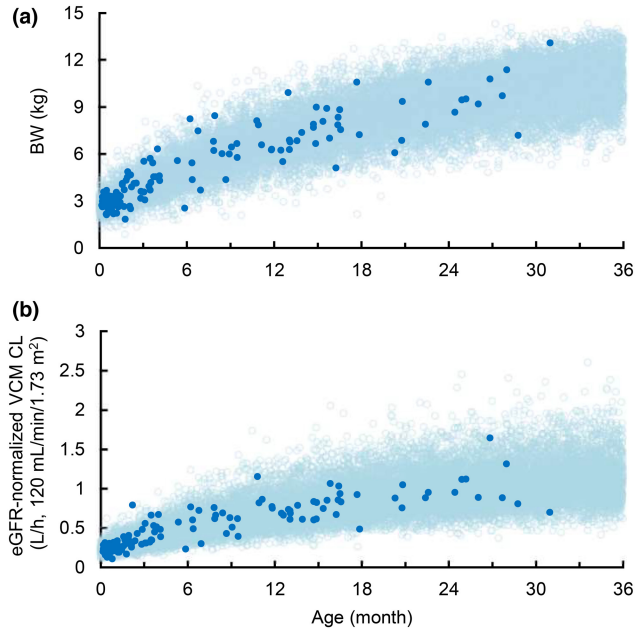

Figure 3 Distributions of body weight (**a**) and eGFR-normalized VCM CL (**b**) in observed and virtual CCHD pediatric patients. Dark blue and pale blue symbols represent the observations in this population and virtual patients (n = 18,000), respectively. BW, body weight; CCHD, critical congenital heart disease; CL, clearance; eGFR, estimated glomerular filtration rate; VCM, vancomycin.

min/1.73 m^2 is shown in **Figure S4**. The virtual CCHD pediatric patients were divided into 2 groups based on age: age ≤ 3 months and 3 months < age ≤ 36 months. No further subdivision of the age groups resulted in > 5% improvement in the target attainment rate. **Figure 4** shows a summary of the dosing simulations for both age groups with eGFR ranging from 20 to 120 mL/min/1.73 m^2. At any given eGFR value in each age group, the target attainment rate was ~ 60% at the recommended dose. The recommended doses are summarized in **Table 3**. The recommended doses for a representative patient in each age group (age ≤ 3 months, eGFR 40 mL/min/1.73 m^2; 3 months < age ≤ 36 months, eGFR 60 mL/min/1.73 m^2) were 25 and 35 mg/kg/day, respectively, which are lower compared with the 60–80 mg/kg recommended dosages based on an AUC/MIC 400–600 in the guidelines.[17]

DISCUSSION

In this study, VCM population PK and the delayed maturation profile of renal CL have been characterized in pediatric patients with CCHD. The age- and renal function-appropriate VCM dosing regimens were determined based on simulations to address the observed delayed renal maturation in children with CCHD.

Congenital heart disease involves structural abnormalities of the heart or great vessels, which occurs during fetal development. Single ventricle physiology is CCHD, which includes hypoplastic left heart syndrome and heterotaxia syndrome results in cyanosis and low cardiac output. In the present study, 37% of the patients had single ventricle physiology and 58% had low cardiac output (2 ventricles). Thus, 95% of the patients exhibited low cardiac output (**Table S2**). Cyanosis results in low blood oxygen levels and reduces the amount of oxygen delivered throughout the body. Low cardiac output results in reduced blood flow to the brain and other vital organs. CCHD affects brain development and abnormal brain maturation in neonates because the brain receives reduced amounts of oxygen-saturated blood from the right ventricle as a consequence of dysfunctional fetal circulation. Neurodevelopmental disabilities affect > 50% of infants with CCHD and involve multiple domains, including motor function, learning, social behavior, and executive function.[28–31] Furthermore, neuroimaging studies using magnetic resonance imaging indicate delayed brain growth and structural brain injury due to a lack of brain oxygen resulting from heart malformations in children with CCHD.[15,32–35]

In the present study, we observed delayed maturation of renal function in children with CCHD based on a PK model for VCM. To our knowledge, there are no previous reports of the maturation of clearance for other renally eliminated drugs or abnormal maturation of kidney function in this population. Nephrogenesis begins in the embryo at approximately week 5 and appears to be anatomically complete at gestation week 36, when there are ~ 1,000,000 nephrons in each kidney.[36] Subsequent maturation is associated with the prolonged maturation of renal tubules, an increase in renal blood flow, and improvement of the filtration coefficient. GFR increased steadily during the first 9 weeks of life.[37] There is rapid maturation of GFR during the early neonatal period, which may be initiated by hemodynamic factors, such as cardiac output, vascular resistance, and mean arterial blood pressure.[38] In the circuitry of the cardiovascular system, the distribution of cardiac output to the kidneys is 25%, which is the highest volume of blood flow compared with the

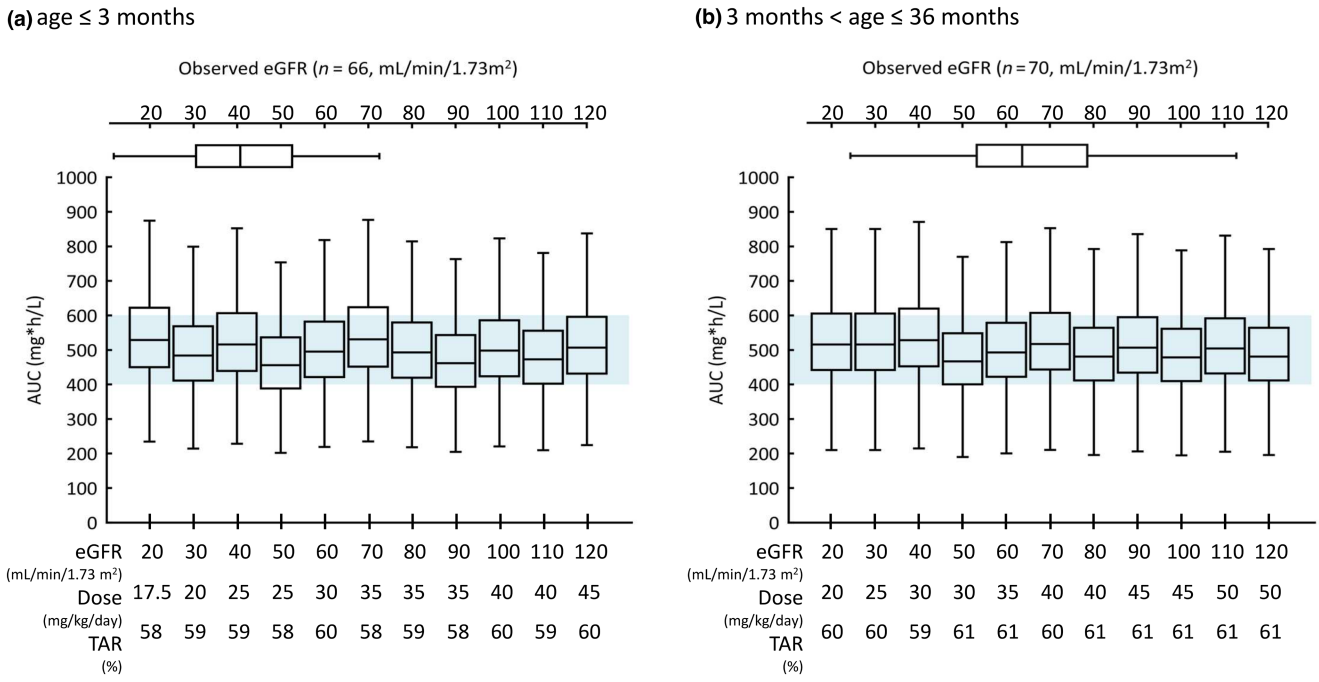

Figure 4 Summary of dosing simulations to virtual CCHD pediatric patients at age ≤ 3 months (**a**) and 3 months < age ≤ 36 months (**b**) at given eGFR values. The top horizontal box plots show the observed eGFR values for each age group. The vertical box plots are AUCs simulated using the dose and eGFR value represented on the *x*-axis. The corresponding TAR percentage is shown at the bottom. AUC, area under the curve; CCHD, critical congenital heart disease; eGFR, estimated glomerular filtration rate; TAR, target attainment rate.

Table 3 Dose recommendation of daily VCM dose (mg/kg/day) for pediatric patients with CCHD

		eGFR (mL/min/1.73 m^2)										
		20	30	40	50	60	70	80	90	100	110	120
Age (months)	≦3	17.5	20	25	25	30	35	35	35	40	40	45
	>3, ≦36	20	25	30	30	35	40	40	45	45	50	50

CCHD, critical congenital heart disease; eGFR, estimated glomerular filtration rate; VCM, vancomycin.

other organs.[39] For fetal physiological-based PK modeling, the percentage of cardiac output to the kidneys is the third highest followed by the brain and lungs.[40] Scholes *et al.*[41] reported that the kidney length of newborns with CCHD on average is larger than normal and renal alternations are present at birth; however, the basis for this increased tissue and its subsequent clinical significance remains unknown. Based on these reports, blood flow to the kidneys is affected by decreased cardiac output resulting from CCHD. Decreased blood oxygen levels in the kidneys due to cyanosis and decreased renal blood flow resulting from low cardiac output may cause delayed maturation and impaired development of renal function. In the present study, VCM CL in pediatric patients with CCHD was lower compared with that predicted by population PK models in non-CCHD pediatric patients (Colin and Kloprogge models; **Figure 2a**). The estimated Hill coefficient for maturation function in this study (1.73 with relative standard error (RSE) 30.1%) was smaller compared with that in both models (2.89 in the Colin model and 3.52 in the Kloprogge model),[23,24] although the difference was not statistically significant due to a relatively high RSE. These results suggested a delayed maturation of renal function in this population.

The recommended VCM dosages for representative children with CCHD based on the final model are 25 and 35 mg/kg/day for patients ≤ 3 months of age with an eGFR of 40 mL/min/1.73 m^2 and 3 months < age ≤ 36 months with an eGFR of 60 mL/min/1.73 m^2, respectively (**Table 3**), and the dosage are considerably lower compared with the 60–80 mg/kg/day dosage in the guidelines.[17] The US Food and Drug Administration (FDA) label recommends the initial dose (for loading) should be no less than 15 mg/kg in patients with any degree of renal impairment to achieve prompt therapeutic drug concentrations,[42] whereas the dose recommendation in this study was a maintenance dose (not for loading) and subsequent dose adjustment by TDM is required.

AUC/MIC simulations using the observed CL in children with CCHD at the lowest guideline-recommended daily dose of 60 mg/kg/day,[17] assuming an MIC of ≤ 1 mg/L exhibited a median of 962.5 (interquartile range: 787.8–1275.0) and 93% of pediatric patients with CCHD with AUC/MIC > 600, suggesting dose optimization for pediatric patients with CCHD to prevent acute kidney injury resulting from overexposure.[17] The recommended dosage for children with CCHD in this study was close to the empiric VCM dosage at our institution (26.4 mg/kg/day; **Table 1**). Children with CCHD following cardiac surgery are at risk for acute kidney injury for many reasons, including low cardiac output syndrome, venous congestion, and impaired kidney perfusion.[16] Moreover, cyanosis and low cardiac output lead to decreased renal blood flow and renal failure,[43,44] and tubular and glomerular injury have been reported in children with CCHD during infancy and early childhood.[45] These findings may explain, in part, the delayed maturation and impaired development in VCM CL observed in this study, which indicates the need for precision dosing in children with CCHD. Dose individualization, based not only on age but on eGFR, using our population PK model contributes model-informed precision dosing for this special population.

The estimated dosing regimens in the present study were lower compared with those previously reported in the same population. Moffett *et al.*[46] found that a dosing regimen of 20 mg/kg/dose every 8 hour (60 mg/kg/day) was most likely to achieve a target AUC/MIC > 400 for children with CCHD following cardiac surgery. The patients examined by Moffett *et al.* received a higher VCM daily dose (43.5 mg/kg/day assuming 8-hour dosing) compared with that observed at our institution (29.2 mg/kg/day assuming 12-hour dosing) to maintain similar trough levels (~ 10–15 mg/L), which resulted in a higher CL estimation (7.86 vs. 4.88 L/h/70 kg). Although patient demographics were comparable, there were some differences between the two studies. In particular, we used a two-compartment model based on rich data, whereas Moffet *et al.* used a one-compartment model with mostly through concentrations. Another reason may be differences in institutional treatment strategies for patients with CCHD, such as anesthetic management during surgery and postoperative management in the intensive care unit, which requires further study.

The strength of this study was that we obtained rich data from patients with CCHD, which represents a rare and unique population. The majority of the data were obtained from children under 3 years old. This enabled us to characterize CL maturation in this unique population of young children, whereas the data from older patients were sparse. Therefore, we performed dosing simulations only for patients under 3 years of age. This may be considered a limitation of the study, but also a limitation of this patient population, as patients with CCHD have a high mortality rate without surgery and most patients receive surgery during their early years of life. It should be noted that our model specifically focuses on the first few years and older patients with CCHD may have different VCM PK properties. Another limitation of this study is that most patients started VCM after cardiac surgery (149 out of 152 patients). Therefore, the potential influence of cardiac surgery on VCM PK[47] could not be entirely distinguished from the effect of disease in this study and the influence of cardiac surgery may contribute to the decreased VCM CL. However, the covariate analyses indicated that the surgery-related parameters (i.e., post operative day (POD), with/without CPB, CPB time, and the lowest body temperature during CPB) did not influence VCM CL, suggesting the observed decreased VCM CL in this population is

likely attributed to the disease population. Further study is warranted to verify the findings in this study and evaluate the renal maturation before cardiac surgery in patients with CCHD.

CONCLUSION

This is the first study to describe the delayed maturation and impaired development of VCM CL in pediatric patients with CCHD. The developed CCHD-specific PK model was used for model-informed dosing simulations to identify age- and eGFR-appropriate dosing regimens in this population. The study highlights the importance of understanding the varying maturation of organ functions to provide precision dosing for young children with rare disease conditions, such as CCHD. Future studies should focus on a prospective evaluation of the developed dosing regimens to validate their effectiveness and safety.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

Y.S., K.F., T.M., H.I., K.K., S.M., and M.O. wrote the manuscript. Y.S. designed the research. Y.S. and H.I. performed the research. Y.S., K.F., and T.M. analyzed the data.

[Correction added on 29 January 2024, after first online publication: The legal statement was changed.]

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