JPPT | Clinical Investigation

Therapeutic Drug Monitoring of Vancomycin in Pediatric Patients With Extracorporeal Membrane Oxygenation Support

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OBJECTIVES Determine pharmacokinetic (PK) parameters and optimal dosage of vancomycin for children on extracorporeal membrane oxygenation (ECMO).

METHODS Retrospective PK study of vancomycin in pediatric patients on ECMO who received IV vancomycin 40 to 60 mg/kg/day every 6 hours. Patients were analyzed according to the presence of acute kidney injury (AKI) and requirement of renal replacement therapy (RRT).

RESULTS Data from 40 children, with a median age of 2.7 years of age (1 month to 14 years) were evaluated. Thirty-two patients (80%) received vancomycin. Vancomycin therapeutic drug monitoring was performed in 29 patients. The subgroup without AKI or RRT were 15. With initial doses, vancomycin trough levels were within therapeutic range in 53% of patients. After dose change, 93% of patients achieved therapeutic levels. The adjusted dose was 40 (34–60) mg/kg/day every 6 hours. Estimated PK parameters were clearance (CL) 1.67 (1–1.67) mL/kg/min; volume of distribution (Vd) 0.73 (0.7–0.9) L/kg; and half-life (t½) 6.2 (4.9–8.06) hours. In the AKI subgroup, 11 patients, the initial median dose was 40 (30–45) mg/kg/day every 8 (6–12) hours. Trough concentrations of vancomycin were within therapeutic range in 27% of patients. After dose modifications, 63% of patients achieved target trough concentration. The final adjusted dose was 20 mg/kg/day (15–30) every 12 (12–24) hours. Estimated PK parameters were Vd 1.16 (0.68–1.6) L/kg; CL 0.83 (0.38–1) mL/kg/min; and a t½ of 23.6 (16.2–31) hours.

CONCLUSIONS In patients without AKI or RRT, Vd of vancomycin was similar and CL was lower compared to pediatric critically ill patients without ECMO. Treatment could be started at 40 mg/kg/day every 6 hours. In patients with AKI, the use of lower doses should be used.

ABBREVIATIONS AKI, acute kidney injury; AUC, area under curve; ECMO, extracorporeal membrane oxygenation; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; RRT, renal replacement therapy; TDM, therapeutic drug monitoring

KEYWORDS acute kidney injury; extracorporeal membrane oxygenation; pediatric; pharmacokinetics; renal replacement therapy; therapeutic drug monitoring; vancomycin

J Pediatr Pharmacol Ther 2018;23(4):305–310

DOI: 10.5863/1551-6776-23.4.305

Introduction

Pharmacokinetic (PK) studies in critically ill patients have shown significant changes in half-life (t½) and volume of distribution (Vd) of a variety of drugs because of physiopathological changes. The effects of sepsis on the PKs or pharmacodynamics (PDs) of antimicrobials have been extensively examined. A major contribution to sepsis-induced changes in PK or PD is due to changes in the Vd and renal clearance (CL) due to hypoperfusion of the kidney. The latter is frequently impaired and this fact may reduce drug elimination.[1] Extracorporeal membrane oxygenation (ECMO) introduces additional variables, such as the type of circuit and systemic inflammation associated with prolonged ECMO that can affect PK of different drugs. Sequestration of drugs in the circuit, increased Vd, and decreased CL are the major PK changes associated with ECMO.[2,3]

Vancomycin is a frequently used first-line agent for treating infections caused by methicillin-resistant *Staphylococcus aureus* or other Gram-positive resistant bacteria.[4] Previous vancomycin PK data in newborns on ECMO have shown an increase of Vd and a decrease of vancomycin CL,[5] but conclusions could not be extrapolated to pediatric patients because organ development and physiological factors affect drug's PK in newborns. Total body water, expressed as percentage of body weight, decreases with age, from approximately 80% in newborns to 60% by 1 year of age; these changes could affect distribution of hydrophilic drugs like vancomycin. In the full-term newborn, glomerular

Table 1. Clinical and Demographic Features of the Study Group

	Patients Without AKI or RRT (n = 15)	AKI Subgroup With or Without RRT (n = 11)	Subgroup With RRT Without AKI (n = 3)
Male, n	11	7	1
Weight, kg*	12 (8–21)	13.5 (8–23)	8 (2.9–23)
Age, mo*	24 (10–100)	42 (12–99)	8 (1–72)
Serum creatinine, mg/dL*	0.22 (0.11–0.3)	0.74 (0.7–1.4)	0.3 (0.3–0.4)
CrCL, mL/min/1.73m²*	158 (144–288)	48 (40–70)	153 (115–160)
Cannulation VV	10	7	2
Cannulation VA	15	4	1
Duration of ECMO, days*	12 (8–25)	12(6–23)	15 (15–21)
RRT, n	0	8	3
Concomitant drugs, n (%)			
Furosemide	6 (40)	3 (27)	1 (33)
Labetalol	3 (20)	2 (18)	1 (33)
Milrinone	9 (60)	7 (64)	2 (67)
Nitroprusside	4 (27)	3 (27)	1 (33)
Survived	13	8	2

CrCL, creatinine clearance; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy; VA, venoarterial; VV, venovenous
* Results expressed as medians and interquartile ranges.

filtration rate is around 10 to 20 mL/min/m² at birth; this increases rapidly to 20 to 30 mL/min/m² during the first weeks of life and typically reaches adult values (70 mL/min/m²) by 3 to 5 months. Neonatal patients with drugs that are mainly excreted by glomerular filtration, like vancomycin, generally require smaller doses or a longer dosing interval.[6] These differences in neonates could reach different results on vancomycin PK than in pediatric patients.

Currently, there are no guidelines on antimicrobial dosing for pediatric patients undergoing ECMO. Dosing strategies are based on recommendations for critically ill pediatric patients, case reports in adults or newborns, and considerations of clinical responses to and plasma concentrations of different drugs. Pediatric patients on ECMO with vancomycin treatment could start, based on published literature, with 20 mg/kg followed by therapeutic drug monitoring (TDM) at 2 and 8 to 12 hours postinfusion.[7] The aim of this study was to determine PK parameters and the optimal dosage of vancomycin for children on ECMO support.

Materials and Methods

This is a descriptive and retrospective study in children admitted to the Pediatric Intensive Care Unit between June 2009 and February 2016 at Clínica Las Condes, Santiago, Chile. Patients younger than 15 years of age requiring ECMO and antimicrobial treatment with vancomycin for suspected or confirmed infection caused by a Gram-positive coccus bacteria were included. Neonates were excluded. This study was approved by the institutional ethics committee.

Clinical information was obtained from the pediatric ECMO database. Patients received a 2-hour vancomycin intravenous infusion, 40 to 60 mg/kg/day every 6 hours. After the second day of treatment, a trough serum concentration was obtained 30 minutes prior to the next dose and repeated according to clinical criteria.

Vancomycin serum concentrations were performed by an immunoenzymatic assay (Cobas c 311, Roche, Hitachinaka-shi, Japan). Dose adjustment was performed by the medical team and/or clinical pharmacists based on the vancomycin serum concentrations.

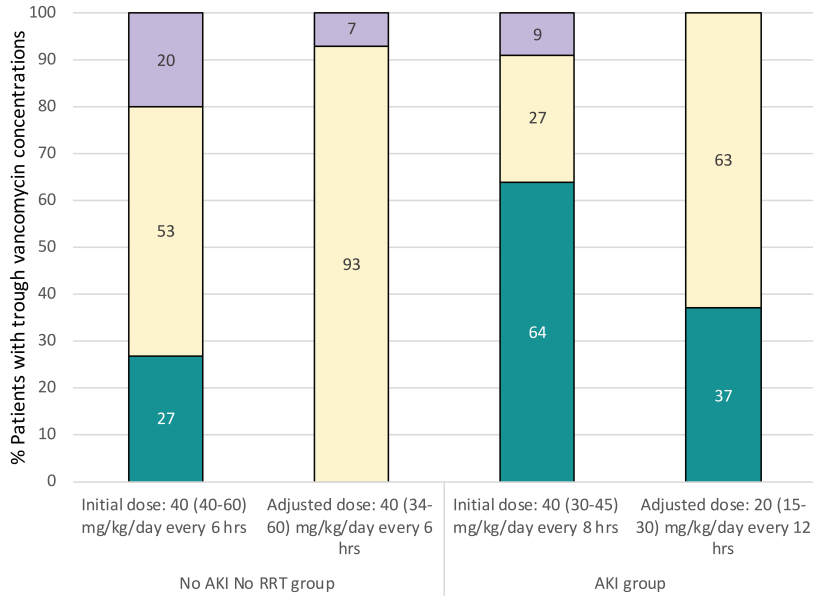
Creatinine CL was estimated with the Schwartz equation. PK parameters were estimated by the Precise PK program through a Bayesian method. For the area under curve/minimum inhibitory concentration estimation (AUC/MIC), a MIC of 1 mg/L for *Staphylococcus aureus* was considered. Patients were analyzed according to the presence of acute kidney injury (AKI) and requirement of renal replacement therapy (RRT) during all the treatment with vancomycin.

Target vancomycin trough serum concentration was defined as 10 to 20 mg/L. AKI was defined as any degree of the pRIFLE classification (pediatric, Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease). Results were expressed as medians and interquartile ranges.

Results

Forty children were included in our study. Thirty-eight

Figure 1. Distribution of patients with trough vancomycin before and after dose adjustment. Patients with vancomycin trough concentrations with initial and adjusted doses. With initial doses, 53% of trough concentrations were within therapeutic range in the group without AKI or RRT and 27% in the group with AKI. After dose adjustment, the percentage of patients with therapeutic trough values increased to 93% and 63%, respectively.



AKI, acute kidney injury; RRT, renal replacement therapy

■ % Patients with supratherapeutic levels; □ % Patients with therapeutic levels; ■ % Patients with subtherapeutic levels

(95%) of these patients were referred from other hospitals. Twenty-five patients (62%) were male, and the median age was 2.7 years of age (1 month–14 years). Thirty-five (87%) patients were connected to ECMO because of a respiratory disease, 3 (8%) because of a cardiac disease, and 2 (5%) for extracorporeal cardiopulmonary resuscitation. Venovenous ECMO was performed in 30 patients and 10 received venoarterial support. The median ECMO duration was 9.5 (7–20.7) days and 33 patients (82%) survived until being discharged.

Thirty-two patients (80%) received vancomycin. The initial dose was 40 to 60 mg/kg/day every 6 hours. Five patients who received vancomycin had a positive culture from a sterile site for a Gram-positive coccus. The remaining patients received empirical treatment. Vancomycin TDM was performed in 29 patients. The clinical and demographic features of the study group are summarized in Table 1.

The subgroup of patients with normal renal function and without RRT totaled 15 (15/29; 52%). The initial median dose was 40 (range: 40–60) mg/kg/day every 6 hours. Vancomycin trough concentrations were within therapeutic range in 8/15 (53%) patients, 4/15 (27%) supratherapeutic values, and 3/15 (20%) had subtherapeutic concentrations. The dose was decreased in all patients with supratherapeutic values. It was also increased in those with subtherapeutic concentrations, reaching everyone's target value, except for one in which vancomycin was halted for clinical reasons. After a single dose change, 14/15 (93%) patients achieved targeted concentrations. The adjusted dose was 40 (34–60) mg/kg/day every 6 hours, with median trough concentrations of 15.8 (13.8–17.7) mg/L.

In the subgroup with AKI with or without RRT (11/29; 38% patients), the initial median dose was 40 (30–45) mg/kg/day every 8 (6–12) hours. Trough vancomycin serum concentrations were within therapeutic range in 3 (27%) patients, 7 (64%) had supratherapeutic values, and 1 (9%) patient had subtherapeutic concentrations. The dose was decreased in the 4 patients with supratherapeutic values, but 3 of them did not achieve target values because of death or treatment being stopped. The patient with subtherapeutic values discontinued treatment before dose adjustment. After 1 or 2 dose modifications, 7 (63%) patients achieved target trough concentrations. The final adjusted dose was 20 mg/kg/day (15–30) every 12 (12–24) hours with 15.95 (12.1–18.03) mg/L trough values. In this subgroup, only 3 patients did not receive RRT. The separate analysis did not affect the global results of the subgroup maybe because of the number of patients without RRT (data not shown).

Figure 1 shows the distribution of patients with vancomycin trough levels before and after dose adjustment. The subgroup with RRT without AKI (3/29; 10% patients)

Table 2. Vancomycin Adjusted Doses and Pharmacokinetic Parameters

	Patients Without AKI or RRT (n = 15)	AKI Subgroup (n = 11)	Subgroup With RRT Without AKI (n = 3)
Adjusted dose, mg/kg/day	40 (34–60) every 6 hr	20 (15–30) every 12 (12–24) hr	40 (30–45) every 6 (6–12) hr
CL, mL/kg/min	1.67 (1–1.67)	0.83 (0.38–1)	1.17 (0.63–1.55)
Vd, L/kg	0.73 (0.7– 0.9)	1.16 (0.68–1.6)	0.88 (0.68–0.92)
t½, hr	6.2 (4.9–8.06)	23.6 (16.2–31)	8.69 (5.05–17.52)
AUC/MIC	502.5 (444–569.1)	462.4 (279.65–538.5)	436.72 (381.7–463.36)

AKI, acute kidney injury; AUC, area under the curve; CL, clearance; MIC, minimum inhibitory concentration; RRT, renal replacement therapy; t½, half-life; Vd, volume of distribution

received 40 (30–45) mg/kg/day of vancomycin every 6 (6–12) hours to achieve therapeutic trough concentrations. PK parameters of the 3 subgroups are shown in Table 2. We analyzed the 3 subgroups to see the relationship between serum creatinine and vancomycin CL. Data are shown in Figure 2.

Discussion

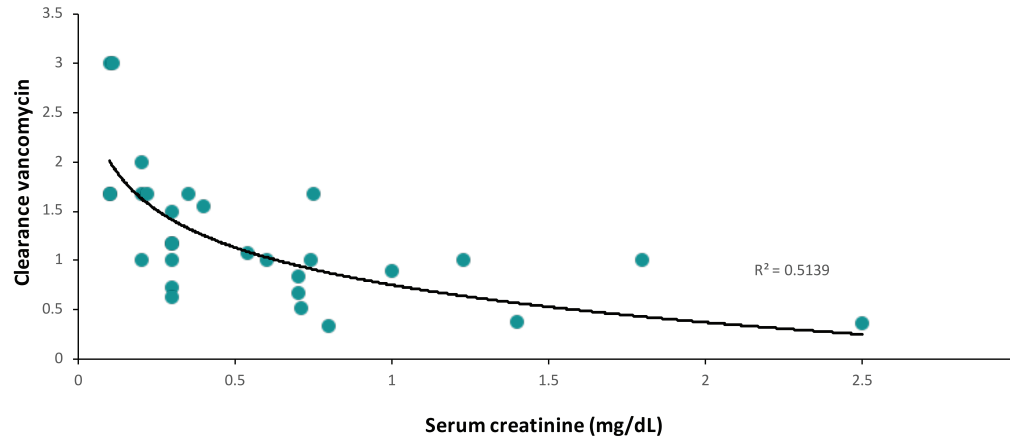
We studied pediatric patients on ECMO, analyzing dosing requirements and PK parameters of vancomycin. In the no AKI and no RRT group, we found a Vd of 0.73 L/kg and a t½ of 6 hours. With a median dose of 40 mg/kg/day every 6 hours, they all achieved an optimal AUC/MIC ratio according to international recommendations that suggest an AUC/MIC > 400.[8]

Mulla et al[9] found in their subgroup of pediatric patients on ECMO a Vd of 0.71 L/kg and t½ of 6.18 hours. Acuña et al[10] found in Chilean pediatric critically ill patients a Vd of 0.62 L/kg but a t½ of 3 hours. Our patients on ECMO without renal injury and no RRT showed similar Vd as previous research but longer t½ than critically ill non-ECMO patients. It is interesting to note, that Mulla et al[9] described PK parameters of vancomycin of pediatric patients on ECMO with different renal function degrees. Our research was the first to analyze vancomycin PK of pediatric critically ill patients on ECMO with normal renal function; this was an important advantage that allowed us to evaluate only ECMO influences on vancomycin PK. Nevertheless, our results were similar to Mulla et al[9] as we found decreased CL and similar Vd of vancomycin compared with pediatric critically ill patients without ECMO support. This could be the basis for recommending lower doses for these patients regardless of renal function.

In order to decrease allergic reactions and maximize duration of catheters, vancomycin is administered over 2 hours in our institution instead of the typical 1-hour infusion that is commonly recommended. This administration could theoretically result in lower peak concentrations and larger Vd than found in other published data. For these reasons, we estimated PK parameters with trough concentrations because we believed that this estimate would not affect the results obtained.

The use of cardiovascular drugs can change vancomycin PK. Because most of the critically ill patients on ECMO need cardiovascular drugs, it is difficult to analyze their effects separately. In our 3 subgroups of patients, the use of these drugs was similar; hence, we

Figure 2. Relationship between serum creatinine and vancomycin clearance. Clearance of vancomycin of the 29 patients was performed with serum creatinine. Vancomycin clearance decreases with higher serum creatinine even in the presence of ECMO support.



assumed this situation as part of the ECMO support.

In the AKI group, smaller doses of vancomycin were required compared with children with normal renal function. A wide variability in the PK parameters were observed; thus, TDM is recommended to individualize an adequate dose regimen. We included patients with different degrees of renal injury and different dialytic techniques, which could modify PK parameters of vancomycin.

Vancomycin CL decreased with higher serum creatinine. When we analyzed the influence of serum creatinine on vancomycin CL, we concluded that vancomycin dosing must be adjusted not only with ECMO support, but that renal function must be assessed before initial dosing.

A limitation of this study was the lack of follow-up because it was retrospective and did not include a control group. However, we did include 29 children on ECMO receiving vancomycin and we could analyze the influence of renal dysfunction and RRT presence. Mulla et al[9] evaluated dosing recommendations in 12 pediatric patients with different renal functions and found larger dosing than occurred in our patients. Different results show that larger, prospective studies are needed for robust dosing recommendations. Of note, because we presented results as interquartile ranges, the total magnitude of dose change was not clearly represented in the subgroup with neither AKI nor RRT. The dispersion of adjusted doses to obtain therapeutic trough concentrations was larger than with initial doses; this is one of the reasons to continue recommending TDM in these patients.

In patients with RRT without AKI, we found that PK parameters were similar to patients lacking AKI and RRT. This would be explained because in this subgroup, nondialytic techniques were implemented for managing fluid balance.

After dose adjustments based on serum vancomycin concentrations, the percentage of patients with therapeutic trough values increased significantly, highlighting the need for TDM in pediatric patients on ECMO. We found a large dispersion of concentrations with initial dosing, even in patients with normal renal function. In order to avoid significant time spent above or below therapeutic targets, mostly in patients with renal dysfunction, it is important to use concentrations obtained early in therapy rather than waiting for a steady-state trough value.

Conclusions

In patients with neither AKI nor RRT, Vd of vancomycin was similar and CL was lower compared with pediatric critically ill patients without ECMO. We recommend initial dosing of 40 mg/kg/day every 6 hours with vancomycin plasmatic levels at 24 hours of treatment for dosing adjustments. In patients with AKI, lower doses should be used according to renal dysfunction. We strongly suggest vancomycin TDM for all pediatric patients on ECMO. Larger and prospective studies are needed to validate recommendations of vancomycin dosing for children on ECMO.

ARTICLE INFORMATION

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data and take responsibility for the integrity and accuracy of the data analysis.

Acknowledgments The authors thank Roberto Dalmazzo, MD; Rodrigo Diaz, MD; Magdalena Castro, RN; Felipe Silva, PharmD; Jorge Morales, PharmD; and the Pediatric Intensive Care Unit residents and nurses for their support and cooperation. Research presented at 35th Annual Meeting of the European Society for Pediatric Infectious Diseases, Madrid, Spain, May 2017; 2nd Latin American ELSO Conference, Cancun, Mexico, December 2016 (First place); XXXIII Congress SOCHINF, Valdivia, Chile, October 2016; and LVI Congress SOCHIPE, Viña del Mar, Chile, October 2016.

Accepted December 13, 2017

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