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Factors affecting serum concentration of vancomycin in critically ill oliguric pediatric patients receiving continuous venovenous hemodiafiltration

지속적 정정맥 혈액투석여과를 적용받는 중증 소아 핍뇨 환자에서 반코마이신의 혈중 농도에 영향을 미치는 인자 분석

2018년 8월

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A thesis of the Master's degree

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Factors affecting serum concentration of vancomycin in critically ill oliguric pediatric patients receiving continuous venovenous hemodiafiltration

August 2018

The Department of Medicine
Seoul National University Graduate School

Bongjin Lee

Abstract

Factors affecting serum concentration of vancomycin in critically ill oliguric pediatric patients receiving continuous venovenous hemodiafiltration

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Background: Vancomycin is known to be unintentionally eliminated by continuous renal replacement therapy, and the protein bound fraction of vancomycin is also known to be different in adults and children. However, there are only a few studies investigating the relationship between the dose of continuous venovenous hemodiafiltration (CVVHDF) parameters and serum concentration of vancomycin in pediatric patients. The aim of this study was to determine clinical and demographic parameters that significantly affect serum vancomycin concentrations.

Method: This retrospective cohort study was conducted at a pediatric intensive care unit in a tertiary university children's hospital. Data from oliguric patients who underwent CVVHDF and vancomycin therapeutic drug monitoring were collected. The correlation between factors affecting serum concentration of vancomycin was analyzed using mixed effect model.

Results: A total of 177 serum samples undergoing vancomycin therapeutic drug monitoring were analyzed. The median age of study participants was 2.23 (interquartile range, 0.3–11.84) years, and 126 (71.19%) were male patients. Serum concentration of vancomycin decreased significantly as the effluent flow rate (EFR; $P < 0.001$), dialysate flow rate (DFR; $P = 0.009$), replacement fluid flow rate (RFFR; $P = 0.008$), the proportion of RFFR in the sum of DFR and RFFR ($P = 0.025$), and residual urine output increased. The adjusted R^2 of the multivariate regression model was 0.874 ($P < 0.001$) and the equation was as follows: Vancomycin trough level (mg/L) = (0.283 × daily dose of vancomycin [mg/kg/d]) + (365.139 / EFR [mL/h/kg]) – (15.842 × residual urine output [mL/h/kg]).

Conclusion: This study demonstrated that the serum concentration of vancomycin was associated with EFR, DFR, RFFR, the proportion of RFFR, and residual urine output in oliguric pediatric patients receiving CVVHDF.

Keywords: children, renal replacement therapy, vancomycin

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List of Abbreviations

BFR, blood flow rate

CRRT, continuous renal replacement therapy

CVVH, continuous venovenous hemofiltration

CVVHD, continuous venovenous hemodialysis

CVVHDF, continuous venovenous hemodiafiltration

ECMO, extracorporeal membrane oxygenation

EFR, effluent flow rate

DFR, dialysate flow rate

ICU, intensive care unit

PICU, pediatric intensive care unit

PFRR, patient fluid removal rate

RFFR, replacement fluid flow rate

TDM, therapeutic drug monitoring

1. Introduction

Vancomycin is the first-choice drug for methicillin resistant *Staphylococcus aureus* infections, and is one of the most frequently used antibiotics in the intensive care unit (ICU) [1, 2]. Since vancomycin is excreted not only through the kidneys but also through continuous renal replacement therapy (CRRT), studies have reported that the serum concentration of vancomycin is affected in patients receiving CRRT [3-7]. In addition, serum vancomycin concentrations are known to be affected by the dose of CRRT [8].

Maintaining an adequate level of antibiotic in patients with infectious diseases is undoubtedly important. Failure to maintain adequate serum levels results in treatment failure or drug toxicity, and for critically ill patients, the outcome may be fatal [6, 7, 9]. Considering that most patients that are administered with vancomycin whilst receiving CRRT are critically ill, maintaining therapeutic serum concentrations of vancomycin is one of the most important factors related to successful treatment outcome in these patients. For this reason, several studies have been conducted on the pharmacokinetics and the optimal dose of vancomycin during the application of CRRT [6, 10-15]. However, most studies have focused on the effects of either hemofiltration or hemodialysis [10, 13]; and there are relatively few studies focused on continuous venovenous hemodiafiltration (CVVHDF) involving the interaction of continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodialysis (CVVHD) [6, 11].

A previous study reported that vancomycin clearance was considerably enhanced with hemofiltration compared to hemodialysis [16]. In contrast, another study reported that the difference in vancomycin clearance was insignificant between hemofiltration and hemodialysis [17]. Another study recommended higher vancomycin doses in patients receiving CVVHD than CVVH, suggesting that vancomycin clearance by hemofiltration was lower than by hemodialysis [12, 15]. Regardless, all of these studies were conducted in adults. Since the protein bound fraction of vancomycin has been reported to be lower in children than in adults [18, 19], there is a limit to applying the results from adult studies directly to children.

Therefore, this study aimed to analyze the relationship between the dose of each CVVHDF parameter and the serum concentration of vancomycin in pediatric patients receiving CVVHDF.

2. Materials and Methods

2.1 Study Population

This retrospective cohort study was conducted at a pediatric ICU (PICU) with 24 beds, in a tertiary university children's hospital. Patients ≤ 18 years old who received CVVHDF and were subjected to vancomycin therapeutic drug monitoring (TDM) at the PICU between January 1, 2005 and August 31, 2015 were included. Samples of vancomycin TDM which the steady-state level of vancomycin was not reached during CVVHDF application were excluded from the study; the steady state was expected to be reached after four or more doses of vancomycin were administered at equal intervals, in accordance with the Infectious Diseases Society of America guideline [20]. Only samples collected for TDM 30 minutes before the administration of vancomycin were included to obtain consistent results [20, 21]. Because extracorporeal membrane oxygenation (ECMO) has significant effects on the hemodynamics of patients and can change the serum concentration of vancomycin, patients receiving ECMO were excluded. Patients without oliguria (urine output ≥ 0.5 mL/kg/h) were also excluded because residual renal function in these patients may enhance the clearance of vancomycin [22].

2.2 Data Collection and Definition

Data on patients' age, sex, serum concentration of vancomycin, daily dose and dosing interval of vancomycin, blood flow rate (BFR), dialysate flow rate

(DFR), patient fluid removal rate (PFRR), replacement fluid flow rate (RFFR), vital signs, fluid input/output balance, residual urine output, and laboratory test results were collected from the electronic medical records. All CVVHDF parameters within 24 hours prior to TDM, and if there were more than 2 values for each of the parameters, their mean value was adopted. Effluent flow rate (EFR) was defined as the sum of DFR, RFFR and PFRR; and the proportion of RFFR was defined as the proportion of RFFR in the sum of DFR and RFFR.

Prisma® or Prismaflex® Systems (Gambro, Lakewood, Colorado, USA) were used for CVVHDF, and polyacrylonitrile (AN69) membrane was used as the hemofilter. Serum concentration of vancomycin was measured using Architect iVancomycin Reagent Kit® (Abbott Laboratories, Chicago, Illinois, USA).

2.3 Statistical Analysis

The correlation between each factor and the serum concentration of vancomycin was analyzed using univariate mixed effect model regression analysis, with patients as random variables and serum concentration of vancomycin as fixed variable. Multivariate regression analysis was performed on the factors that showed significant results in the univariate regression analyses, and the model was determined by backward selection method. In the multivatiate regression model, adjustment of the statistical significance was made using Bonferroni correction, and the overall type I error rate was 0.05. All statistical analyses were performed using R version 3.4.3 (R Foundation for statistical computing, Vienna, Austria).

2.4 Ethics Statement

The Seoul National University Hospital Institutional Review Board approved the study protocol (H-1508-138-697) and waived the need for written informed consent.

3. Results

3.1 Baseline Characteristics of Patients

Patients who underwent vancomycin TDM while receiving CVVHDF at the PICU during the study period were screened. A total of 177 samples of vancomycin TDM from 75 patients were included in the final analyses based on the inclusion and exclusion criteria (Fig 1). The median age was 2.23 (interquartile range, 0.3–11.84) years old, and 126 (71.19%) samples were obtained from male patients. Table 1 shows the baseline characteristics of the samples included.

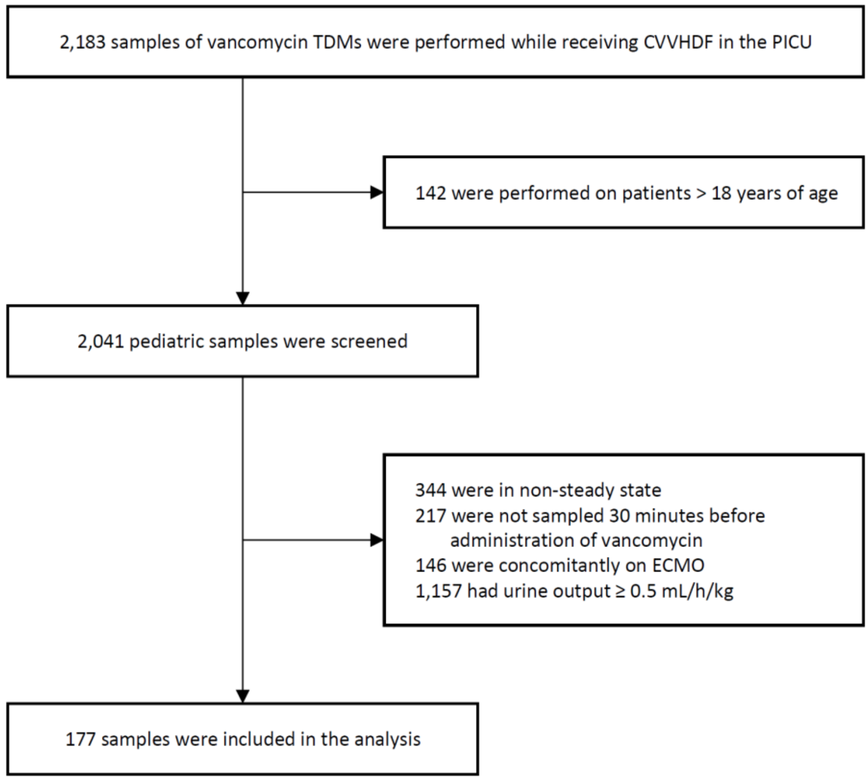

Figure 1. Flow chart of the study population
TDM, therapeutic drug monitoring; CVVHDF, continuous venovenous hemodiafiltration; PICU, pediatric intensive care unit; ECMO, extracorporeal membrane oxygenation

Table 1. Baseline characteristics and the relationship between each characteristic and the trough level of vancomycin

	No. of samples (N=177)	Estimate	SE	*P*
Age (years)	2.23 (0.3–11.84)	-0.254	0.259	0.33
Sex				
Female	51 (28.81)	Reference		
Male	126 (71.19)	3.73	3.337	0.267
Height (cm)	73.7 (57–128.8)	-0.042	0.036	0.248
Weight (kg)	12.3 (4.9–27.8)	-0.015	0.088	0.868
Body surface area (m^2)	0.5 (0.28–0.97)	-1.793	3.35	0.594
Underlying disease				
Cardiovascular disease	58 (32.77)	Reference		
Gastrointestinal disease	8 (4.52)	-1.244	7.746	0.873
Genitourinary disease	22 (12.43)	0.173	5.592	0.975
Hemato-oncologic disease	35 (19.77)	6.165	4.718	0.194
Immunologic disease	13 (7.34)	-1.061	6.965	0.879
Infectious disease	12 (6.78)	3.852	5.979	0.521
Neurologic disease	3 (1.69)	-3.457	8.981	0.702
Respiratory disease	24 (13.56)	-2.632	4.912	0.594
Others[a]	2 (1.13)	3.25	7.953	0.684
Administration of vancomycin				
Daily dose of vancomycin (mg/kg/d)	20.11 (15.42–29.81)	0.185	0.041	<0.001
Dosing interval of vancomycin (h)	12 (12–12)	-0.443	0.089	<0.001
Trough level of vancomycin (mg/L)	12.3 (9.4–16.6)	NA	NA	NA
CVVHDF dose				
BFR (mL/min/kg)	4.13 (3.22–6.88)	-0.373	0.214	0.085
DFR (mL/h/kg)	26.99 (23.58–34.88)	-0.175	0.065	0.009
PFRR (mL/h/kg)	4.73 (3.29–6.5)	-0.22	0.229	0.339
RFFR (mL/h/kg)	23.81 (12.73–39.13)	-0.089	0.033	0.008
EFR (mL/h/kg)	57.05 (46.26–72.73)	-0.097	0.027	<0.001
Proportion of RFFR[b]	0.45 (0.29–0.57)	-6.102	2.668	0.025
Vital signs and clinical findings				
Systolic blood pressure (mmHg)	98 (93–99)	-0.07	0.049	0.154
Diastolic blood pressure (mmHg)	52 (45–60)	-0.053	0.048	0.271
Heart rate (beat/min)	128 (114–142)	0.021	0.041	0.614
Respiratory rate (breath/min)	39 (30–47)	-0.134	0.077	0.085
Body temperature (℃)	36.45 (36.3–36.97)	-0.144	1.366	0.916
Fluid input-output balance (mL/kg)	12.11 (-19.33 to 36.19)	0.002	0.008	0.854
Residual urine output (mL/h/kg)	0.03 (0–0.12)	-16.237	6.355	0.012
Laboratory findings				
Leukocyte ($\times 10^3/mm^3$)	11.83 (7.24–18.19)	0.024	0.055	0.669
Total protein (g/dL)	6.3 (5.5–7.2)	-0.081	0.614	0.895
Albumin (g/dL)	3.56 (3.18–4.29)	0.649	0.948	0.495
C-reactive protein (mg/dL)	5.32 (2.33–13.94)	0.061	0.101	0.545
Procalcitonin (ng/mL)	2.4 (1.73–6.69)	0.08	0.098	0.422

Continuous data are presented as median (interquartile range), and categorical

data as n (%).
SE, standard error; NA, not applicable; CVVHDF, continuous venovenous hemodiafiltration; BFR, blood flow rate; DFR, dialysate flow rate; PFRR, patient fluid removal rate; RFFR, replacement fluid flow rate; EFR, effluent flow rate
[a]Drug intoxication and skin necrosis due to extravasation of intravenous drug were included in this disease category.
[b]Proportion of RFFR in DFR + RFFR

3.2 Factors Affecting Serum Concentration of Vancomycin

Univariate analyses showed that daily dose and dosing interval of vancomycin, DFR, RFFR, EFR, the proportion of RFFR, and residual urine output were significantly related to serum concentration of vancomycin. As the daily dose of vancomycin ($P < 0.001$) increased, and dosing interval of vancomycin ($P < 0.001$), DFR ($P = 0.009$), RFFR ($P = 0.008$), EFR ($P < 0.001$), the proportion of RFFR ($P = 0.025$), and residual urine output ($P = 0.012$) decreased, the serum concentration of vancomycin increased (Table 1, Figs 2A and 2B).

Multivariate analysis was performed on the significant variables found in the univariate analysis. The multivariate model derived from backward selection had four predictor variables including daily dose of vancomycin ($P < 0.001$), dosing interval of vancomycin ($P < 0.001$), EFR ($P = 0.019$), and residual urine output ($P < 0.001$). However, the *P*-value of dosing interval of vancomycin was greater than the corrected *P*-value 0.0125 through the Bonferroni method, and the final model was as follows (adjusted $R^2 = 0.874$, $P < 0.001$) (Table 2, Fig 2C):

Vancomycin trough level (mg/L) = (0.283 × daily dose of vancomycin [mg/kg/d]) + (365.139 / EFR [mL/h/kg]) − (15.842 × residual urine output [mL/h/kg]).

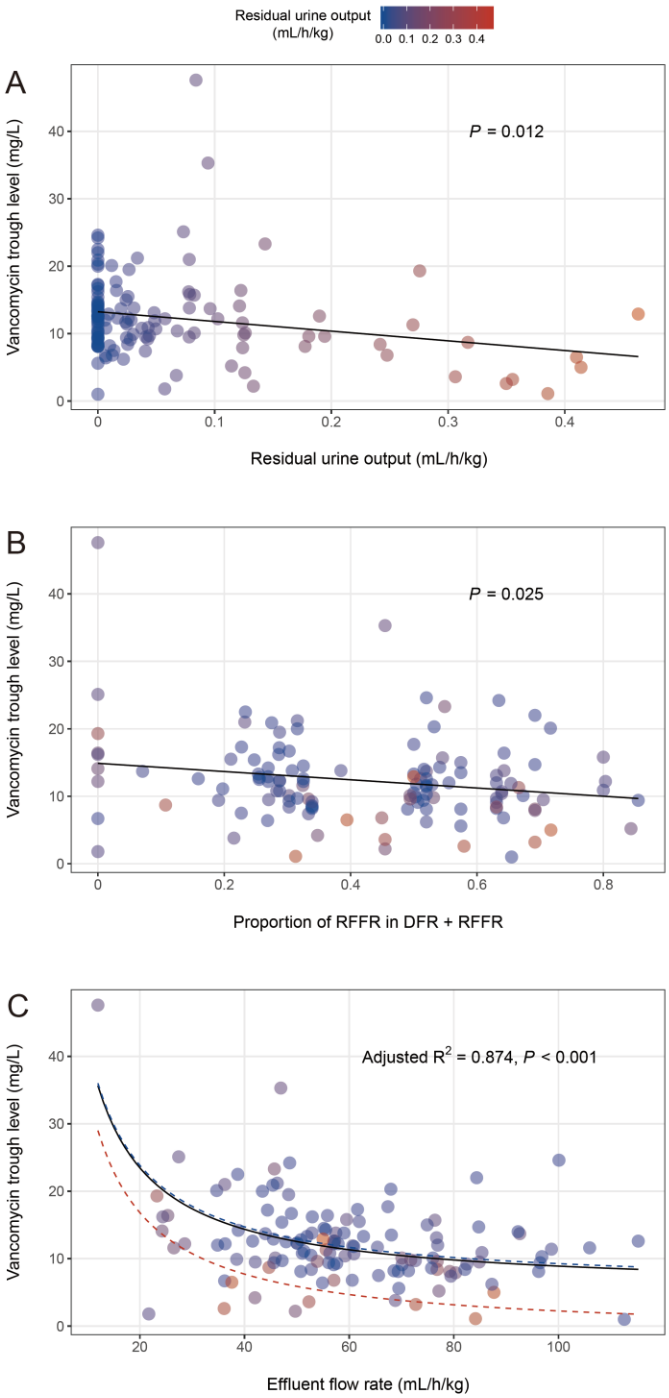

Figure 2. Scatterplots of the vancomycin trough level and its associated factors.

The color of the spots indicate residual urine output (mL/h/kg). When the residual urine output is 0, it is blue, and when it is closer to 0.5, it is red. (A)

Scatterplot of the residual urine output and vancomycin trough level showing a regression line (y = -16.24x + 17.60). (B) The line represents a linear regression line between proportion of RFFR and vancomycin trough level, with the formula 'y = -6.102x + 14.889'. (C) The curves obtained by substituting the median value (20.11 mg/kg/d) for 'daily dose of vancomycin' in a multivariate regression model (Vancomycin trough level [mg/L] = 0.283 × daily dose of vancomycin [mg/kg/d] + 365.139 / effluent flow rate [mL/h/kg] – 15.842 × residual urine output [mL/h/kg]). The black solid curve is obtained by inputting 0.03 (mL/h/kg) as the median value in the residual urine output. The minimum value of 0 (mL/h/kg) is shown as a blue dashed curve, and the maximum value of 0.46 (mL/h/kg) is shown as the red dashed curve

Table 2. Relationship between each characteristic and the trough level of vancomycin (multivariate mixed effect model regression analysis)

Characteristics	Estimate	SE	*P*
Daily dose of vancomycin (mg/kg/d)	0.283	0.035	<0.001
EFR (mL/h/kg)	365.139	38.655	<0.001
Residual urine output (mL/h/kg)	-15.842	4.312	<0.001

SE, standard error; EFR, effluent flow rate

3.2 Vancomycin trough level group comparison

The samples of vancomycin TDM were divided into 4 groups (less than 10 mg/L, between 10–15 mg/L, between 15–20 mg/L, and 20 mg/L or more) according to their vancomycin trough levels. The doses of EFR ($P = 0.001$), DFR ($P = 0.031$), RFFR ($P = 0.017$), and residual urine output ($P = 0.014$) were significantly lower in the groups with a higher vancomycin trough level. On the contrary, PFRR showed no significant difference according to the groups (Table 3, Figs 3A and 3B).

Table 3. Relationship between vancomycin trough level group and each factor.

CVVHDF parameters	Vancomycin trough level groups				*P*
	< 10 mg/L (n = 47)	≥ 10 and < 15 mg/L (n = 49)	≥ 15 and < 20 mg/L (n = 15)	≥ 10 mg/L (n = 14)	
EFR (mL/h/kg)	68.82 (51.53–78.17)	57.05 (50.06–68.06)	52.95 (45.77–61.76)	45.56 (36.23–48.63)	0.001
DFR (mL/h/kg)	27.03 (24.04–38.09)	26.99 (23.81–35.48)	29.31 (21.34–32.3)	24.54 (18.04–28.46)	0.031
RFFR (mL/h/kg)	24.72 (14.3–43.29)	23.81 (12.89–39.5)	12.73 (11.33–31.9)	16.39 (8.12–29.66)	0.017
PFRR (mL/h/kg)	4.85 (3.31–6.82)	4.9 (3.29–6.14)	3.96 (3.3–6.97)	4.51 (3.69–5.7)	0.425
Residual urine output (mL/h/kg)	0.04 (0–0.16)	0.01 (0–0.05)	0.02 (0–0.08)	0.01 (0–0.08)	0.014

Data are presented as median (interquartile range).
CVVHDF, continuous venovenous hemodiafiltration; SE, standard error; EFR, effluent flow rate; DFR, dialysate flow rate; RFFR, replacement fluid flow rate; PFRR, patient fluid removal rate

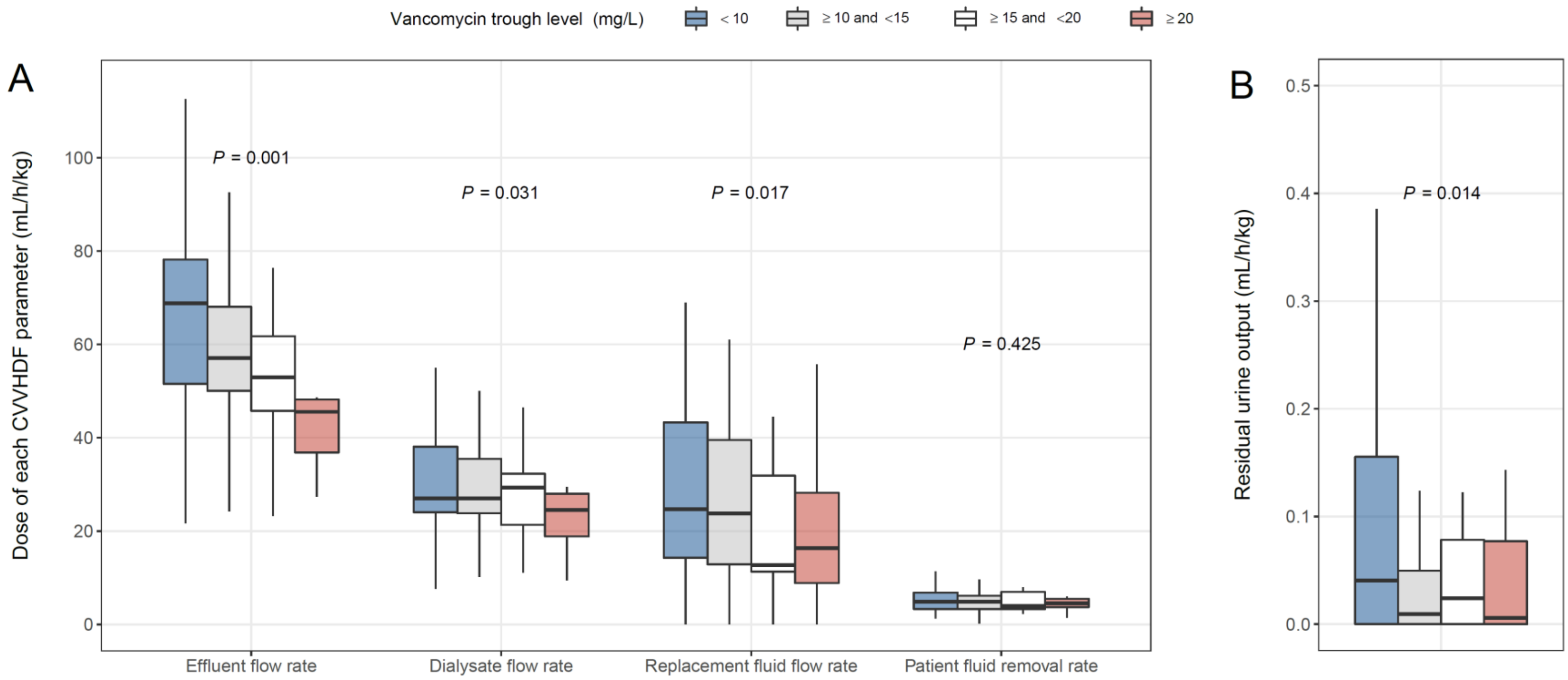

Figure 3. The dose of each CVVHDF parameter and residual urine output according to the vancomycin trough level groups.
(A) The vancomycin trough levels were divided into 4 groups. The dose for each vancomycin trough level group was shown according to each CVVHDF parameter. (B) Residual diuresis showed a significant difference according to vancomycin trough level group.
CVVHDF, continuous venovenous hemodiafiltration

4. Discussion

This study was designed to analyze clinical and demographic parameters, to observe which parameters affect the serum concentration of vancomycin. The data analyzed from 177 pediatric samples of vancomycin TDM over a ten-year period demonstrated that DFR, RFFR, EFR, the proportion of RFFR, and residual urine output were significantly related to the serum concentrations of vancomycin.

In this study, the serum concentration of vancomycin decreased with increasing EFR, DFR, and RFFR. This is consistent with previous researches showing that vancomycin is excreted via hemofiltration and hemodialysis, and that the intensity of RFFR and DFR correlated with the clearance of vancomycin [5, 7, 13, 23-26]. It is also consistent with previous studies that show EFR to be a reliable predictor of antibiotic concentration in patients receiving CVVHDF [8, 27]. In the past, due to the use of low-flux hemofilter, drug clearance by CRRT, especially hemodialysis, was influenced by the size of drug molecule. However, in the recent years, high-flux hemofilters have replaced low-flux hemofilters, therefore having almost no influence on drug clearance according to the size of the drug molecule [3, 13]. Because all samples of vancomycin TDM included in this study received CVVHDF with a high-flux hemofilter AN69 [28, 29], it is possible that vancomycin could be effectively excreted by hemodialysis.

As the proportion RFFR increased, that is, the ratio of hemofiltration to hemodialysis increased, the serum concentration of vancomycin decreased significantly. This is in agreement with studies reporting that vancomycin is more effectively excreted by hemofiltration than by hemodialysis [16], but contrasts studies that recommend a higher vancomycin dose for patients receiving CVVHD or CVVHDF than CVVH [12, 15]. Because many factors related to the pharmacokinetics of vancomycin interact with each other in critically ill patients receiving CRRT [30], convection and diffusion may act in synergy with each other, causing an improved convection and over diffusion [11]. However, it is difficult to make a simple comparison with these studies, and in addition, the aforementioned studies were conducted on adults. It is known that the protein binding faction of vancomycin is significantly lower in children than in adults [18, 19]. Therefore, the possibility that vancomycin clearance by CVVHDF may be affected by the difference in the pharmacokinetic characteristics of vancomycin in these children compared with adults should be considered carefully.

In this study, to diminish the effect of residual renal function on vancomycin trough level, samples with urine output ≥ 0.5 mL/kg/h were excluded from the analyses. Nevertheless, even though the residual urine output was negligible, vancomycin trough levels were significantly affected. This is consistent with previous studies in which residual diuresis has been reported to affect serum drug concentration in patients undergoing CRRT [31, 32]. The therapeutic range of vancomycin is recommended to be 10–15 mg/L for non-severe infections and 15–20 mg/L for severe infections [33, 34]. Therefore, even if a non-severe infection is assumed, levels below 10 mg/L are in the subtherapeutic range. In the present study, 47 samples within the subtherapeutic range accounted for 26.55%, showing a relatively large proportion of the study samples. The median value of the vancomycin dose used in this study was 20.11 mg/kg/day, which is approximately the same as the recommended dose (20 mg/kg/day) for patients receiving CVVHDF. However, it is speculated that vancomycin was actually excreted by residual diuresis as well as CVVHDF. This is supported by the fact that patients with a higher the residual urine output had lower vancomycin trough levels, and most of the patients with a higher residual urine output was observed in the subtherapeutic group.

Although vancomycin clearance in patients receiving CVVHDF appears to be easily predicted by the known principles of hemofiltration, hemodialysis, and pharmacokinetic properties of vancomycin, it is recommended that TDM be performed instead of relying only on the predicted value because the actual clinically measured value is often different from the predicted value [3, 7, 8, 14, 35, 36]. In particular, vancomycin has a narrow therapeutic range, thus accurate prediction and maintenance of proper serum concentration are more important [20, 21]. For these reasons, the necessity of research based on actual clinically obtained results, as well as experimental research has emerged; and in fact, such clinical studies have been carried out [8, 30]. Nevertheless, only a few clinical researches include data on children. This study is significant in that there is no data comparing the proportion of hemofiltration and hemodialysis which affects the serum concentration of vancomycin in children receiving CVVHDF.

This study has several limitations. First, because this study was a retrospective study, controlling all the variables to exclude bias was difficult, and incomplete data restricted the extent of the study. An example being the duration of hemofilter use, which may have affected vancomycin clearance. However, we were unable to obtain this information. Second, this study derived a model through multiple regression analysis. However, this formula was not validated for external validity. And if population pharmacokinetics were used, a more optimized model could be derived. Finally, this study was conducted at a PICU in a single center, and therefore caution is needed when applying the results of this study to other centers. Nevertheless, data obtained from this study can be the basis for future prospective studies. Also, it is important for bringing awareness to the necessity of studies on children receiving CVVHDF.

4.1 Conclusions

In conclusion, this study demonstrated that serum concentration of vancomycin was associated with EFR, DFR, RFFR, the proportion of RFFR, and residual urine output in oliguric pediatric patients receiving CVVHDF. A well-designed multicenter study is needed to draw conclusions that are more specific and applicable at a broader level.

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국 문 초 록

반코마이신은 지속적 신대체요법을 통해서 의도치 않게 체외로 배설될 수 있으며, 소아에서는 반코마이신의 단백질 결합 비율이 성인과 다른 것으로 알려져 있다. 지속적 정맥 혈액투석여과(continuous venovenous hemodiafiltration, CVVHDF) 요법시 반코마이신 농도에 대한 연구는 매우 드물며, 소아를 대상으로 한 연구는 없어 본 연구를 계획하였다. 따라서 본 연구의 목적은 CVVHDF를 적용 받는 소아 핍뇨 환자에서 혈중 반코마이신 농도에 유의하게 영향을 미치는 인자들에 대해 분석하는 것이다.

본 연구는 후향적 코호트 연구로서 2005년부터 2015년까지 서울대학교병원 소아중환자실에 입실하여 CVVHDF를 적용 받는 중에 반코마이신 치료적 약물 감시(therapeutic drug monitoring, TDM)를 받은 18세 이하의 핍뇨 환자를 대상으로 하였다.

177건의 반코마이신 혈중 농도 표본이 분석되었고, 전체 대상자의 연령 중위수는 2.23세(interquartile range, 0.3–11.84)였으며, 126 (71.19%) 표본은 남자였다. 혈중 반코마이신의 농도는 유출액 속도 (effluent flow rate, EFR; P < 0.001), 투석액 속도 (dialysate flow rate, DFR; P = 0.009), 대체용액 속도 (replacement fluid flow rate, RFFR; P = 0.008), RFFR의 비율 (P = 0.025), 그리고 잔뇨량이 증가함에 따라 유의하게 감소하는 결과를 보였다. 다변량 회귀 분석 모델의 보정된 R^2 값은

0.874 ($P < 0.001$)이었으며, 회귀식은 다음과 같았다: 반코마이신 최저치(mg/L) = (0.283 × 반코마이신 투여량[mg/kg/d]) + (365.139 / 유출액 속도[mL/kg/min]) – (15.842 × 잔뇨량[mL/kg/h]).

본 연구를 통하여 CVVHDF를 적용받는 소아 핍뇨 환자에서 혈중 반코마이신 농도에 영향을 미치는 인자는 유출액 속도, 투석액 속도, 대체용액 속도, 대체용액 속도의 비율, 그리고 잔뇨량임을 알 수 있었다.

주요어: 소아, 신대체요법, 반코마이신

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