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Therapeutic Drug Monitoring of Vancomycin in Severe Patients with COVID-19 for Optimizing Drug Dosage

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Abstract

Background: For unknown pharmacokinetic (PK) parameters and higher drug toxicity of vancomycin in severe patients with coronavirus disease 2019 (COVID-19).

Objective: To optimize vancomycin dose through performing therapeutic drug monitoring (TDM).

Methods: A observational study was performed between Feb 11, 2020 and Mar 23, 2020. Serum samples (n = 63) from eight patients intravenously vancomycin with or without nasal administration were collected. Drug concentrations were analyzed by ultra-performance liquid chromatography-tandem mass spectrometry. Vancomycin dosage was adjusted depending on drug concentration. A population PK model was developed using NONMEM software. Therapeutic effects, and vancomycin-related adverse events were monitored.

Results: The mean trough and peak concentration were 13.79 ± 6.61 (4.63-34.2) mg/L (n = 36) and 30.97 ± 9.71 (17.0-49.9) mg/L (n = 27), respectively. 25.4% of serum vancomycin concentration was beyond optimal range (< 10 mg/L at trough or > 40 mg/L at peak). Dose adjustments were made for 3 patients. Significant difference ($P < 0.05$) was detected in peak concentrations before and after dose adjustment. The PK of vancomycin was consistent with two-compartment model, with the clearance and distribution volume in the central compartment of 4.3 L/h and 2.0 L, respectively. The AUC_{0-24}/MIC of vancomycin was 848 ± 566 h. At early treatment, 60% (3/5) of patients with normal baseline renal function developed acute kidney injury. After dosing adjustment based on TDM, no vancomycin-associated nephrotoxicity was detected. The targeted infection was clinically cured in all patients.

Conclusion: TDM of vancomycin in patients with COVID-19 are necessary to optimize drug dosage. Based on our PK model, its clearance was 4.3 L/h.

Keywords

LC-MS, Therapeutic drug monitoring, Pharmacokinetics, Coronavirus disease 2019, Vancomycin

Introduction

Since December 2019, a novel coronavirus disease (COVID-19) has been spreading rapidly all over the world, and become a big challenge to people [1-3]. Secondary bacterial infections were general [4-7], in 7% of hospitalised COVID-19 patients [5], and 31% of patients who required invasive mechanical ventilation and in 50% of non-survivors [6]. Gram-positive bacteria

including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococci* (MRCNS) and *Enterococci* species are common nosocomial pathogens, which mainly cause ventilator-associated pneumonia (VAP) [8-10]. Vancomycin 15 mg/kg intravenous injection (IV) per 8-12 h with or without a loading dose was recommended for treating such infections [11-13]. However, due to the narrow treatment window and individual biological differences, sub-optimal vancomycin concentrations were prevalent, leading to insufficient antibacterial potency or increased risk of acute kidney injury [14-21]. Therefore, it is necessary to perform therapeutic drug monitoring (TDM) of vancomycin for optimizing clinical dosing [22,23], in order to ensure its clinical effect while minimizing the occurrence of adverse reactions [19,24-28]. For severe MRSA infection, the guidelines recommended a ratio of 24-hour area under the concentration time curve and minimum inhibitory concentration (AUC_{0-24}/MIC) of 400 to 600 in both adult and pediatric patients to maximize the anti-bactericidal activity and minimize acute kidney injury (AKI) risk [29-31]. Because AUCs are not routinely available in clinical practice, plasma or serum concentration is also used as substitute [32-35]. The guidelines of the Chinese Pharmacological Society recommended a serum trough level of 10-15 mg/L in adult patients and 10-20 mg/L for serious MRSA infections [26,35,36]. Furthermore, the peak concentration was expected to be less than 40 mg/L [37,38].

Since the mass hospitalization of patients with COVID-19, including a high proportion relying on mechanical ventilation, it might increase vancomycin usage for treating hospital-acquired infections, especially ventilator-associated pneumonia (VAP) [39,40]. However, there was little knowledge about the pharmacokinetics of vancomycin inpatients with COVID-19. The decision of drug dosage relied on clinical experiences or expert opinions. Therefore, in this study, we performed TDM of vancomycin by ultra performance liquid chromatography/tandem mass spectrometry (UHPLC-MS/MS) [41-43] in patients with COVID-19. Doses were optimized according to drug concentration.

Methods

Study design and patients

The study was performed in Shanghai Public Health Clinical Center (SPHCC, Shanghai, China), a designated hospital for patients with COVID-19. Laboratory confirmation of COVID-19 was made as previously reported [44].

The clinical management of COVID-19 was adherent to the Chinese management guideline for COVID-19 (version 6.0) [45]. Gram-positive bacterial infection was diagnosed according to the guidelines [11,46]. Cultures were carried out as described previously [47-49]. *Staphylococcus* species were cultured in Luria-Bertani medium [48] and *Enterococcus* species were in Brain Heart Infusion Agarmedium [49]. Vancomycin usage (initial dosage, total duration of intravenous or administered via nasogastric tube) was decided by an expert panel of infectious disease and critical care, in adherence to the relevant guidelines [11,50]. Data on serum drug concentrations were sent to the clinicians within 8 hours after blood collection. Doses were adjusted by a panel of experts, based on TDM and renal function data. Pathogen clearance was defined as negative conversion of culture after treatment. Acute kidney injury (AKI) was defined and graded according to the KDIGO clinical practice guidelines [51-53]. Co-administration of vancomycin administration via nasogastric tube to prevent *Clostridium difficile* colonitis [54] was also recorded.

TDM of vancomycin was requested by the clinicians. The blood samples were collected within 0.5 h before the fourth continuous IV of vancomycin (trough spot) and 0.5-1 h after infusion (peak spot) [55,56]. Similar blood collecting time for vancomycin administration via nasogastric tube was used. At each spot, 2 mL of blood was drawn into a non-anticoagulant tube, treated with acetonitrile (ACN) solution to inactivate the virus, and centrifuged. The volume of serum used for TDM was 50 µL per test. The normal concentration range was set at 10-20 mg/L for the trough [57,58] and 20-40 mg/L for the peak [32,38,59].

The study protocol was reviewed and approved by the Ethics Commission of SPHCC (No. YJ-2020-S053-02), registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn, NO:ChiCTR2000035629), and all the procedures were performed in accordance with the recommendations of the Declaration of Helsinki on biomedical research involving human subjects. Informed consent was acquired from the patients or their surrogates.

Measurement of vancomycin levels

Vancomycin concentrations were detected by UHPLC-MS/MS as previously reported [32,60,61]. Briefly, fifty microliters of serum were precipitated with 360 µL acetonitrile (ACN) solution (50 µL 10% formic acid, 10 µL demethylvacomycin (IS) (50 mg/L)and 300 µL ACN). The operations were carried out in the BSL-2 laboratory. After precipitation, the supernatant was sent to the analytical laboratory, diluted for 20-fold with 5% ACN solution, and detected by UHPLC-MS/MS.

The UHPLC system consisted of a Waters Acquity UPLC (Waters Corporation, Milford, USA) and an AB Sciex Triple Quad 5500 (AB SCIEX company, Boston, USA).

Chromatographic separation of vancomycin and its IS was carried out on an ACQUITY UPLC HSS C18 column (2.1 mm × 100 mm, 1.8 μm) (Waters Corporation, Massachusetts, USA). Chromatographic separation was performed using a mobile phase composed of 0.1% FA (A) and methanol containing 0.1% FA (B). The analytes were detected by multiple reactions monitoring (MRM) mode with ion pairs of *m/z* 725.5/144.2 for vancomycin and *m/z* 718.4/144.2 for IS. The line range was 1-100 mg/L.

Population PK (PPK) and pharmacokinetic/pharmacodynamic (PK/PD) analysis

PPK model was developed to describe the time profiles of vancomycin pharmacokinetic characters using NONMEM (Ver7.4, ICON Co. Ltd, USA), PsN (Ver4.7, Uppsala University) and Xpose software (Ver4.5, Uppsala University). The base model was two-compartment model as shown in Figure 1.

There is no absorption process for intravenous vancomycin. X_1 and X_2 were drug amount in the central and peripheral compartment, respectively. CL was clearance from the central compartment, while Q was the inter-compartment clearance between the central and peripheral compartment. V_1 and V_2 were distribution volume in the central and peripheral compartment, respectively. Model equations for evaluation of candidate covariates are as follows:

$$\begin{cases} \dfrac{dX_1}{dt} = f_{ivgtt} + f_{Nasal} - \dfrac{CL}{V_1}X_1 - \dfrac{Q}{V_1}X_1 + \dfrac{Q}{V_2}X_2 \\ \dfrac{dX_2}{dt} = \dfrac{Q}{V_1}X_1 - \dfrac{Q}{V_2}X_2 \\ f_{ivgtt} = \begin{cases} AMT_{ivgtt} / D_{ivgtt} & t \le D_{ivgtt} \\ 0 & t > D_{ivgtt} \end{cases} \\ f_{Nasal} = \begin{cases} AMT_{Nasal} / D_{Nasal} & t \le D_{Nasal} \\ 0 & t > D_{Nasal} \end{cases} \\ C = \dfrac{X_1}{V_1} \end{cases}$$

f indicated input function. D_{Nasal} and D_{ivgtt} indicated the duration of drug in the absorption and infusion, respectively. AMT was drug dose, and C was vancomycin concentration in central compartment. Inter-subject variability (IIV) of CL was consistent with the exponential model, while IIV of other parameters were fixed as zero. The residual error model was consistent with the proportional model.

The following covariates were tested during development of the final PPK model: gender, age, weight, serum creatinine, estimated glomerular filtration rate, urea nitrogen, alanine aminotransferase, direct bilirubin, body temperature, hemodialysis, extracorporeal membrane oxygenation (ECMO) and concurrent use of levofloxacin and/or caspofungin. A fixed-effect model was developed using stepwise method. The covariate would be included in the model if the decrease of objective function value (OFV) was greater than 3.84 ($P < 0.05$) in the forward selection, or the increase of OFV was greater than 6.63 ($P < 0.01$) in the backward elimination. The type of covariate model tested included power model or linear model. Individual PK parameters of vancomycin were obtained using Bayesian feedback method. For Bayesian software programs can be used to generate accurate and reliable estimates of the daily AUC values with trough-only PK sampling.

The PPK model was simulated 100 times using the final estimates. Mean concentration was calculated using individual prediction data. The daily AUC_{0-24} was calculated using trapzoidal area method after the first dose each day. The average AUC_{0-24} was obtained according to sum (AUC_{0-24})/(treatment duration-days without drug administration). The AUC_{0-24}/MIC was calculated as the ratio of mean AUC_{0-24} to MIC [62]. These were performed using Matlab software (Ver7.0.1, Math works Co. Ltd, USA).

The correlation between AUC_{0-24}/MIC and the microbiological effect of vancomycin was analyzed. To analyze the relationship between AUC_{0-24} and AKI occurrence, logistic regression and cross tabulation were used to find the critical value which could differentiate the AKI occurrence with maximal probability.

Statistical analysis

Graphpad Prime 5.0 (GraphPad Software, San Diego, California) was used to compare vancomycin concentrations, and create a scatter plot. The curve of concentration for vancomycin, estimated glomerular filtration rate (eGFR) and serum creatinine level were obtained by using OriginPro 70 software (OriginLab, Massachusetts, USA). The Student t test (and Nonparametric test) was used to compare the concentration levels. All tests were 2-tailed. A P value < 0.05 indicated statistical significance.

Results

Baseline characteristic and outcome of patients with COVID-19

Among the all 368 patients hospitalized in Shanghai public health clinical center from Feb 11, 2020 to Mar 23, 2020, eight (2.17%) received intravenous vancomycin treatment. TDM was conducted for all eight patients based on the clinical requirement (Table 1 and Table S1). The median age was 64.5 (57-81) years, including

Table 1: The clinical and experimental characters of 8 patients enrolled from Feb 11, 2020 to Mar 23, 2020.

No.	Age (Year)	Sex	Pathogen	MIC mg/L	Infection site	ECMO	Hemodyalysis on Baseline	Baseline Creatinine	Baseline eGFR	Initial Dose	Nasal feed vancomycin	Therapy duration (Total/IV/Pre.)*	Sub-optimal/total troughs	Overdose/total peaks	Ctrough/Cpeak	Adjust dose	Pathogen Clearance	AKI	AUC0-24 (h·mg/L)	AUC0-24/MIC (h)
1	64	M	*Staphylococcus haemolyticus*	2	Lung	Yes	No	71.77	101.39	1000 mg Q12 h	250 mg Q6 h	28/28/5	4/16	2/14	4.63-23.6/17-47.7	Yes	Yes	1	676	338
2	81	M	*Enterococcus faecalis*	2	Bloodstream	Yes	Yes	188.67	31.7	1000 mg Q12 h	250 mg Q6 h	39/5/3	5/13	3/9	5.9-34.2/21.8-49.9	Yes	Yes	NA	488	244
3	62	M	*Enterococcus faecium*	≤ 0.5	Lung	Yes	No	77.4	92	1000 mg Q12 h	No	25/25/4	0/1	0/0	11.8/NA	No	Yes	NA	456	912
4	75	M	*Enterococcus faecium*	≤ 0.5	Lung	Yes	Yes	85.62	80.13	500 mg Q8 h	250 mg Q6 h	17/13/4	0/3	1/1	19.5-26.6/41.7	Yes	Yes	3	869	1738
5	57	F	*Staphylococcus haemolyticus*	1	Bloodstream	No	No	46.88	107.93	1000 mg Q12 h	250 mg Q6 h	13/12/2	0/1	1/1	12.1/41.43	No	Yes	NA	370	370
6	70	M	*Staphylococcus haemolyticus*	1	Lung	No	Yes	79.82	88.09	1000 mg Q12 h	No	11/11/3	0/1	0/0	15.1/NA	No	Yes	NA	984	984
7	63	F	Emperical (NA)	NA	Lung	Yes	No	31.67	193.99	1000 mg Q12 h	125 mg Q6 h	11/10/6	0/1	0/1	14.3/34.8	No	NA	2	457	NA
8	65	M	*Enterococcus faecium*	≤ 0.5	Lung	No	Yes	146.48	43.37	1000 mg Q12 h	No	5/5/5	0/0	0/1	NA/24.6	No	Yes	NA	674	1349
Mean																			622	848
SD																			218	566

six males and two females (Table 1 and Table S1). Seven (87.5%) patients had a clear etiology, including four cases with *Enterococcus faecium* pneumonia, and three with *Staphylococcus haemolyticus* bacteremia.

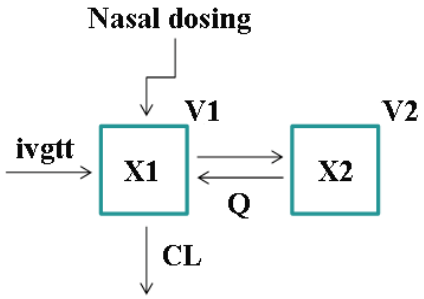

Figure 1: The base model of two-compartment for vancomycin.

X_1 and X_2 were drug amount in the central and peripheral compartment, respectively. CL was clearance from the central compartment, while Q was the inter-compartment clearance between the central and peripheral compartment. V_1 and V_2 were distribution volume in the central and peripheral compartment, respectively.

Circles mean actual data. Red line means local weighted regression line, while blank line means unity line (a) or zero horizontal line (b).

The rest one received empirical vancomycin treatment for pneumonia. At baseline, each of them was on invasive mechanical ventilation. During the therapeutic process, 5 (62.5%) were on Extracorporeal Membrane Oxygenation (ECMO), and 4 (50%) were on hemodyalisis. The baseline creatinine concentration and eGFR were 91.04 (31.67-188.67) μmol/L and 92.33 (31.7-193.99) mL/min, respectively. Seven out of 8 have basic diseases such as hypertension, and renal dysfunction (Table S1). The initial vancomycin dosage was 1000 mg every 12 hours (1000 mg Q12 h) in six patients, 500 mg per 8 hours (500 mg Q8 h) in one and 1000 mg every 24 h (1000 mg Qd) in the last patient. Five of them were also administered vancomycin through nasogastric tube feeding. The median treatment duration (including nasal administration) was 18.6 (5-39) days. All 7 culture-confirmed infection turned negative after vancomycin treatment. Among patients who did not receive hemodialysis at baseline, 50% (2/4) experienced AKI, including one initiated hemodialysis 4 days after vancomycin treatment.

Vancomycin concentration determination by UHPLC-MS/MS

Vancomycin concentrations were detected by

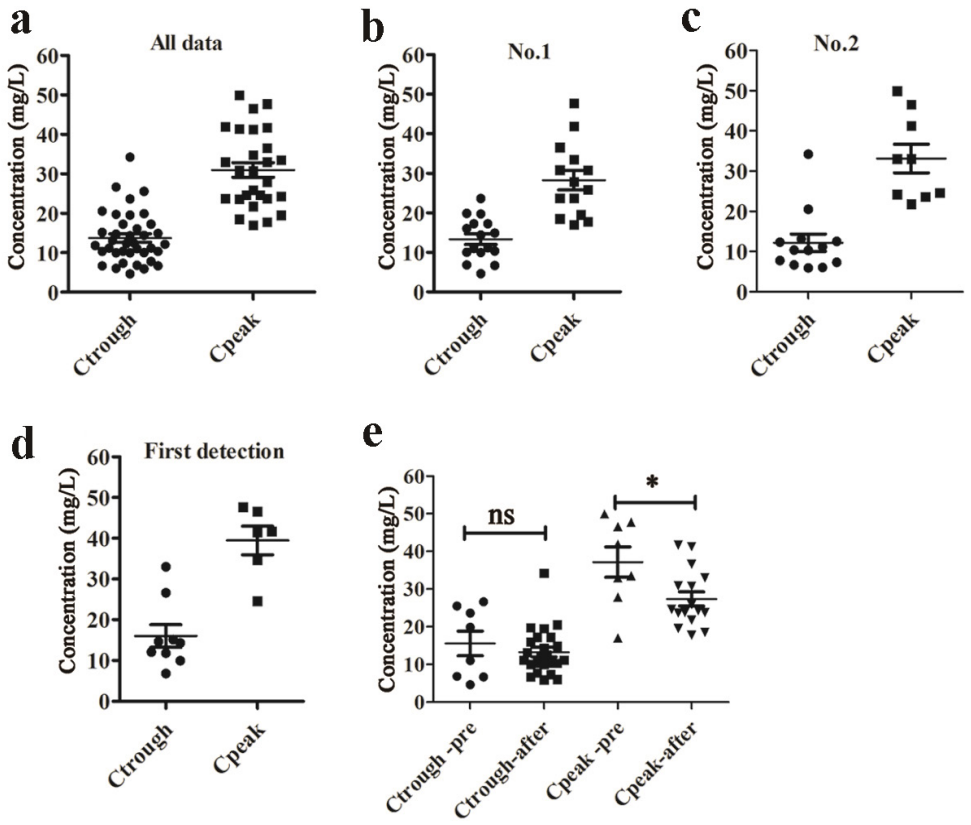

Figure 2: Monitoring of serum vancomycin concentration in patients with COVID-19 (a) All data from 8 patients; (b and c) The data from patient No. 1 and patient No. 2, respectively; (d) The data from the first detection of all patients; (e) Comparison between the concentration before and after dose adjustments.

$P < 0.05$ represents statistical difference; ns-no statistical difference; *- $p < 0.05$.

UHPLC-MS/MS. Method validation was performed according to Food and Drug Administration (FDA) guidelines [63], including linearity, selectivity, etc. The intra- and inter-day precision of vancomycin were less than 15%. The accuracy ranged from 93.00% to 107.00%. The matrix effects of vancomycin normalized by IS was 97.92 in higher quality control (HQC) and 101.50% in lower QC (LQC). The Extraction recovery of vancomycin was 101.70% in HQC, and 99.40% in LQC. The relative standard deviation (RSD) in matrix and extraction recovery of vancomycin were all less than 15%. As shown in Supplement (Figure 1 and Figure S1), vancomycin and IS were eluted at about 1.77 min. The endogenous substances in the blank serum did not interfere with vancomycin and IS (Figure S1A and Figure S1B). The compounds eluted from healthy donors (Figure S1C and Figure S1D) were similar to those from COVID-19 patient's samples (Figure S1E and Figure S1F).

TDM of vancomycin in patients with COVID-19

A total of 63 time-spots were monitored, including 36 troughs and 27 peaks (Table S1 and Table 1). Out of the 36 trough samples, nine had concentrations less than 10 mg/L and 5 have concentrations greater than 20 mg/L. Of the 27 peak samples, seven had concentrations more than 40 mg/L, and 4 less than 20 mg/L. The mean trough concentration was 13.79 ± 6.61 (4.63-34.2) mg/L (n = 36) and the peak concentration was 30.97 ± 9.71 (17.0-49.9) mg/L (n = 27) (Figure 2A). For patients with available samples on peak or trough, 28.6% (2/7)) patients had at least one trough concentration less than 10 mg/L, and 80.0% (4/5) of the patients had at least one peak concentration greater than 40 mg/L. Of which, patient No. 1 and 2 patients were monitored for 14 and 21 days, respectively, and thus, more samples were collected from them than from the others, who had

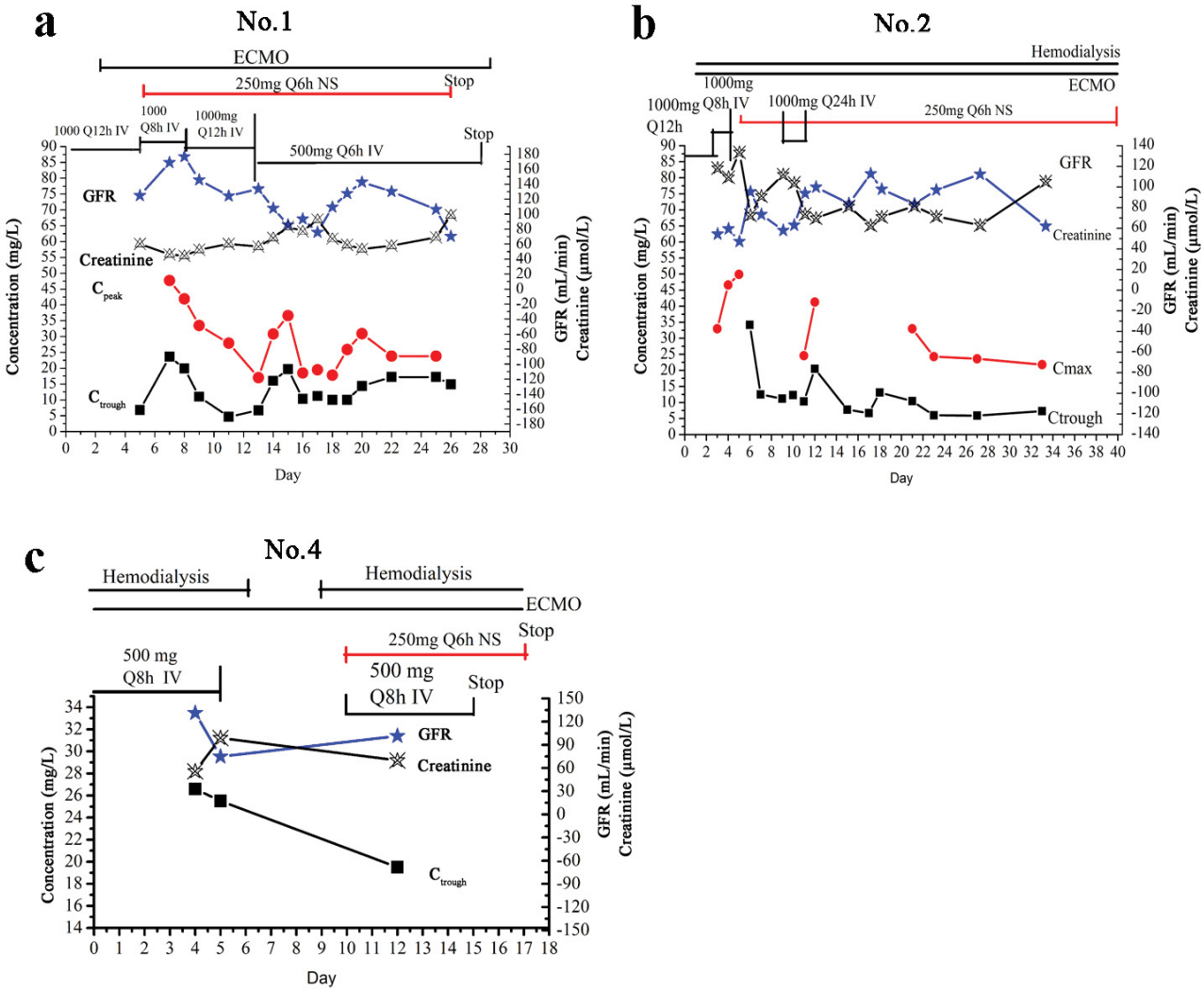

Figure 3: The curve of concentration for vancomycin, GFR, and creatinine from three patients with dose adjustments (a) From No. 1 patient; (b) From No. 2; (c) From No. 4. Intravenous administration (IV) shown in dosing and blank line; vancomycin administration via nasogastric tube (NS) shown in dosing and red line. Square frame and blank curve: C_{trough}; Circular dots and red line: C_{peak}; Star and blue line: GFR; Star and blank line: $C_{reatinine}$. The date giving loading dose was counted as day 0, and the data for vancomycin stopping as "stop". ECMO and Hemodialysis were shown from loading dose to drug stopping.

one to four samples (Table S1). For No. 1, five samples showed trough concentrations beyond the normal range (10-20 mg/L) and two samples showed higher peak concentration (> 40 mg/L) (Figure 2B). For patient No. 2, 10 samples (50%) were out of normal range, including 7 at trough and 3 at peak (Figure 2C).

Furthermore, we examined the data from the first test of each patient, and found that 50% (3/6) of peak concentrations were higher than the upper limit of 40 mg/L with a mean of 37.2 (24.6-47.7) mg/L. Furthermore, 42.9% (3/7) of the trough concentrations were also beyond the recommended range (10-20 mg/L) with a mean of 17.3 (6.8-34.2) mg/L (Figure 2D).

Dose adjustment dependent on drug concentration

Dose adjustment of intravenous vancomycin was made for three (37.5%) patients (No. 1, 2 and 4) according to their serum drug concentrations. After dose adjustments, the peak concentrations (28.3 (17.0-49.9) mg/L (n = 20)) were basically returned to normal range. Significant difference ($P < 0.05$) was detected in peak concentrations before and after dose adjustment (Figure 2E).

The curve of concentration for vancomycin, GFR, and creatinine from three patients with dose adjustments was shown in Figure 3 (Figure 3A for patient No. 1, Figure 3B for patient No. 2, Figure 3C for patient No. 4). Patient No.1 (Figure 3A) was initiated with intravenous vancomycin at 1000 mg per 12 h to treat *Staphylococcus haemolyticus*. On day 5, at first detection, C_{trough} was 6.8 mg/L lower than 10 mg/L. The intravenous dose was then increased to 1000 mg Q8 h. He was also given vancomycin via nasogastric tube at 250 mg Q12 h from day 7. C_{peak} was 47.7 and 41.9 mg/L on day 7 and day 8, respectively. Intravenous dose was decreased to 1000 mg Q12 h on day 8, and C_{trough} was 4.63 mg/L and 6.7 mg/L on day 11 and day 13, respectively. Intravenous dose was further adjusted to 500 mg Q6 h on day 13. Since then, optimal drug concentration was detected with 90% (9/10) of samples on trough spots and 100% (9/9) on peak spots. However, he met the criteria of grade 1 AKI on day 28 and then stopped intravenous vancomycin.

Patient No. 2 (Figure 3B) was initiated with intravenous vancomycin at 1000 mg Q12 h to treat *Enterococcus faecalis* bacteremia. He presents with renal dysfunction and was on hemodialysis since baseline. At first detection on day 3, C_{peak} was 33.0 mg/L and intravenous dose was adjusted to 1000 mg Q8h according to improved eGFR. However, C_{peak} rised to 46.6 mg/L on day 4, then on the same day intravenous vancomycin was stopped. He also received vancomycin via nasogastric tube from day 5 to day 39. From day 5 to day 12, C_{peak} and C_{trough} gradually returned to normal. He was given 1000 mg Q24h of vancomycin intravenously on day 9 and stopped on day 11, when both C_{peak} and C_{trough} exceeded the expected range. From day 15 to day 33, C_{trough} was 5.9-13.1 mg/L and C_{peak} was 21.8-33.0 mg/L, although the patient was only given vancomycin via nasogastric tube.

Patient No. 4 (Figure 3C) was initiated with intravenous vancomycin at 500 mg Q8h to treat *Enterococcus faecium* pneumonia. On day 4 and 5, C_{trough} was 26.6 mg/L and 25.5 mg/L, respectively. After that, vancomycin administration was paused till day 10, when the patient was given intravenous vancomycin at 500 mg Q8 h and vancomycin via nasogastric tube at 250 mg Q6 h. On day 12, C_{trough} and C_{peak} were 19.5 mg/L and 41.7 mg/L, respectively. Intravenous vancomycin was stopped on day 15, after the blood culture results were negative.

Population PK and pharmacokinetic/pharmacodynamic (PK/PD) analysis

The PK parameters of vancomycin were shown in Table 2 CL and Q were 4.3 L/h and 4.1 L/h, and V_1 and V_2 were 2.0 L and 56.7 L respectively. Half-life for distribution phase and elimination phase was 10 min and 19 h, respectively. Hemodialysis and serum creatinine level were covariates on the CL. Both of them were consistent with the power model. The CL in patients with hemodialysis decreased by 58% compared to those in patient without hemodialysis. IIV of CL was removed because it was close to zero after adding hemodialysis and serum creatinine level as the covariates. ECMO did

Table 2: Vancomycin PK parameters in the final PPK model

Parameter (Unit)	Explain	Value (RSE%)
CL (L/h)	Clearance from central compartment	4.33 (23.8%)
V_1 (L)	Distribution volume in central compartment	2.00 (62.3%)
Q (L/h)	Inter-compartment clearance between central and peripheral compartment	4.14 (68.4%)
V_2 (L)	Distribution volume in peripheral compartment	56.7 (36.3%)
D_1 (h)	Duration during drug absorption	1.90 (6.0%)
θ_{Hemo}	Impact factor of hemodialysis on the clearance	0.42 (13.5%)
θ_{Scr}	Impact factor of serum creatinine on the clearance	0.41 (20.5%)
ε (%)	Proportional residual error item	31.3 (5.7%)

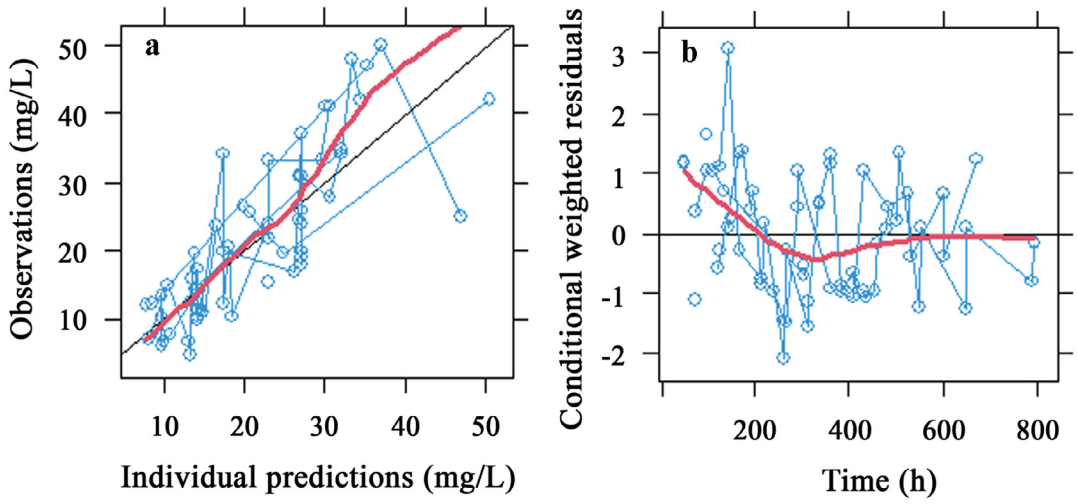

Figure 4: Diagnostic plot of final PPK model of vancomycin (a) Comparing individual predictions to observations; (b) The correlation coefficient between conditional weighted residuals and time.

not have significant effect on vancomycin PK parameters. As shown in Figure 4A, individual predictions were close to observations. The correlation coefficient reached 0.81. Most of conditional weighted residuals distributed evenly across zero horizontal line (Figure 4B), indicating that the model estimates were reliable and stable.

The AUC_{0-24} of vancomycin was shown in Table 1. The mean ± SD were 622 ± 218 h·mg/L, and coefficient of variation was 35%. If the vancomycin dose was higher, or the drug was given more frequent, the AUC_{0-24} would increase. For example, in patient No.1, AUC_{0-24} changed from 871 to 740 h·mg/L when the dosage changed from 1000 mg Q8h IV + 250 mg NS (day 5-7) to 1000 mg Q12h IV+ 250 mg NS (day 8-11). The AUC_{0-24} changed from 596 to 945 h·mg/L when the dosage changed from 1000 mg Q12h IV (day 0-2) to 1000 mg Q8h IV (day 3) in patient No. 2.

AUC_{0-24}/MIC of vancomycin was shown in Table 1. The mean ± SD was 848 ± 566 h·mg/L, and coefficiency of variation was 67%. The maximum and minimum of AUC_{0-24}/MIC were 1738 and 244 h·mg/L, respectively. Although AUC_{0-24}/MIC for 3 patients was less than 400, the microbiological effects were all successful. There was no correlation between AUC_{0-24}/MIC and microbiological effect (R^2 = 0.01). AUC_{0-24} had a positive correlation with the grade of AKI. AUC_{0-24} = 675 h·mg/L was the best critical value for differentiating AKI occurrence. When $AUC_{0-24} \geq 675$ h·mg/L, 2 of 3 patients (67%) had AKI. Meanwhile, When $AUC_{0-24} < 675$ h·mg/L, only 1 of 5 patients (20%) had AKI (p = 0.19).

Discussion

A previous study reported secondary infection in 15% of hospitalized patients with COVID-19 [8]. Gram positive bacteria were the major pathogens in hospitalized (especially ventilated) patients. The rapid increase in hospitalization and ventilation, associated with COVID-19, highlighted the need for vancomycin usage in treating gram positive bacterial infections in these patients [6]. Rational usage of vancomycin relies on TDM, in order to maintain an optimal concentration, and reduce the risk of treatment failure, drug resistance, as well as renal injury. Here we presented pilot findings of TDM in patients with COVID-19.

Renal dysfunction, hemodialysis and ECMO usage were major factors that affected the PK of vancomycin [64]. Among eight participants with COVID-19, six (except No. 1 and 5) (75%) had at least one of these factors at baseline. The clinical characters of these 8 patients indicate that comorbidities might increase acute kidney injury or COVID-19 (critical illness) could be a factor of acute kidney injury, implying the difficulty in the rationale of vancomycin usage among these severepatients. 25.4% (16/63) of serum concentration of vancomycin was beyond optimal range (< 10 mg/L at trough or > 40 mg/L at peak) [65]. At early treatment, 60% (3/5) of patients with normal baseline renal function developed acute kidney injury. These highlighted the necessity of TDM for vancomycin treatment in patients with COVID-19.

Abnormal concentration especially for peak spots was more prevalent in samples at the beginning than after initiation of TDM (vs. $P < 0.05$). After dose adjustment in three patients with abnormal trough and/or peak concentrations, it returned to and maintained within the safe and effective range. Target infection was clinically cured in 7 of the patients (one is emperical treatment), and no vancomycin-associated nephrotoxicity was detected during TDM process. TDM could be a useful tool to guide the proper usage of vancomycin in patients with COVID-19.

Although vancomycin was generally considered to be nonabsorbable through gastral administration [66], there were a few case reports of 'red man syndrome' [67,68], ototoxicity or encephalopathy related to oral vancomycin [68,69]. In this work, we detected a distinct and stable serum concentration for 20 days in one patient during vancomycin administration via nasogastric tube alone after stopping intravenous usage. This indicated that gastral vancomycin might be absorbed. Gastral vancomycin is often used to treat or prevent *Clostridium difficile* infection among ventilated patients, who might be numerous in the COVID-19 pandemic. Further study and special attention are needed to determine the potential toxicity and drug resistance induced by gastral vancomycin usage in patients with COVID-19, especially those who produce detectable serum concentrations.

During the development of base model, we found that OFV for one-compartment model was higher than that for two-compartment model. Parameter D1 was always near to its boundary in the one-compartment model. Hence, we chose two-compartment model as the structure for base model. In the development of fixed-effect model, we found that, if the combination with tigecycline and meropenem were chosen as the covariates on CL, this will also decrease OFV from 300.5 to 281.7 significantly ($P < 0.001$). However, this model could not be explained from the PK point of view. Therefore, we used the covariates hemodialysis and serum creatinine level as the covariates in the final PPK model.

The PK of vancomycin was consistent with two-compartment model, which was consistent with the previous reports [70,71]. Since renal function for some patients decreased (especially patient No. 2 and No. 8), the half-life for distribution phase was longer than the previous report (19 h vs. 12 h) [72]. Our study showed that no impact of ECMO on the PK of vancomycin, which was consistent with other two reports [73,74].

AUC_{0-24}/MIC has been identified as the most suitable PK/PD index for the efficacy of vancomycin. For the MRSA infections, the recommended range of AUC_{0-24}/MIC in the guideline is between 400 and 600 assuming a MIC of 1 mg/L [29]. The pathogens in the patients with COVID-19 in this study were MRCNS and *Enterococci*. Although the average AUC_{0-24}/MIC of No. 1, 2 and 5 patients was less than 400, microbiological clearance was still achieved in each of them. This was consistent with the results of a prospective study in Chinese adult subjects [70]. The target value of AUC_{0-24}/MIC for clinical/microbiological efficacy in Chinese adult patients may be between 200 and 300. Our study showed that AUC_{0-24} with value 675 h·mg/L may be the critical value for differentiating AKI occurrence. This was similar to a report which showed that $AUC_{0-24} \geq 650$ h·mg/L was the cut point for AKI occurrence [75].

This study had certain limitations. First, being an observational study involving only 8 patients rather than a multicenter randomized controlled trial, the data of this study should be used cautiously when applying to larger populations and different settings. Second, we found considerable serum concentration in one patient during the period of vancomycin administration via nasogastric tube alone. This data along with its clinical significance need to be further verified in larger cohorts. Third, vancomycin concentration was tested with the serum samples alone, which does not best represent the concentration in key organs such as the lung and kidney. Fourth, we did not test the covariates for basic disease and concomitant usage of drugs except for antibiotics. The fitting of PPK model might be improved if these data were analyzed additionally. Fifth, relative standard error for V_1 and Q of vancomycin were relatively high (~60%) because the number of data in the PPK analysis was not so plenty. Last but not least, due to the small number of participants, this study did not find a correlation between AUC_{0-24}/MIC and efficacy in the patients with COVID-19.

Conclusions

An UHPLC-MS/MS method was developed to quantify vancomycin concentration. Sixty-three serum samples were tested and 16 samples had a concentration beyond the expected range (< 10 at trough and > 40 mg/L at peak). TDM guided dosage adjustment in 37.5% of the patients, leading to an optimal concentration. All patients were cured and no vancomycin-associated nephrotoxicity was detected after dose adjustment according to TDM. PK was consistent with two-compartment model, and CL was affected by hemodialysis and renal function. Vancomycin AUC_{0-24} had positive correlation with AKI occurrence, while AUC_{0-24}/MIC did not have correlation with the efficacy. In summary, TDM could be a useful approach or tool to guide the optimizing dose of vancomycin in patients with COVID-19.

Ethical Consideration

The ethical approval has been obtained from the ethics committee of Shanghai Public Health Clinical Center.

Human and Animal Rights

No animals were used in this study. All human research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki Principles of 1975, as revised in 2013 (http:/ethics. iit. Edu.ecodes/node/3931).

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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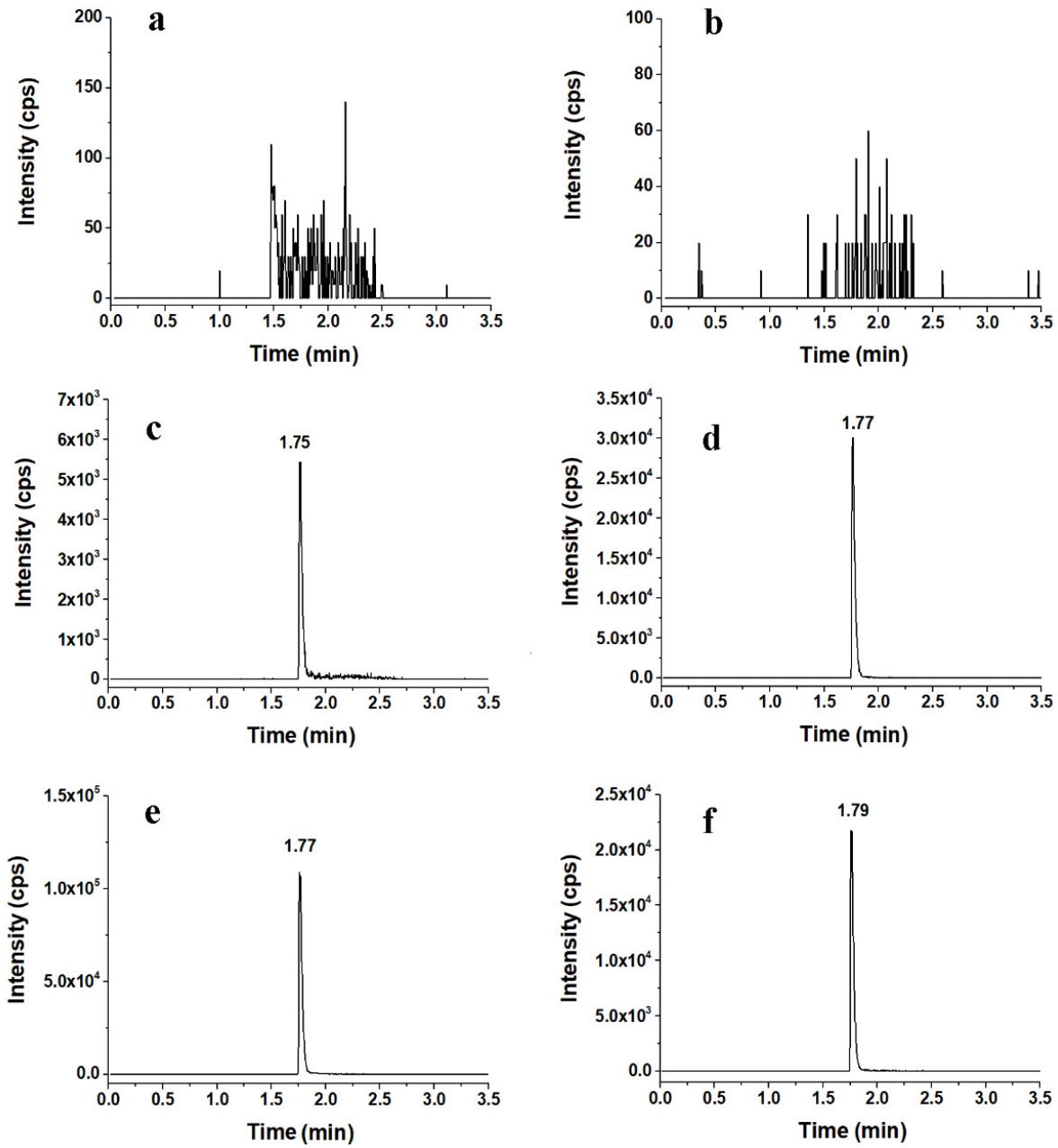

Figure S1: MRM chromatograms of vancomycin and internal standard (a and b) were vancomycin and IS spectrogram in blank serum; (c and d), spiked blank serum with vancomycin and IS at the concentration of LLOQ (1 mg/L for vancomycin, and 10 mg/L for IS); (e and f) vancomycin and IS spectrogram from COVID-19 patient sample.