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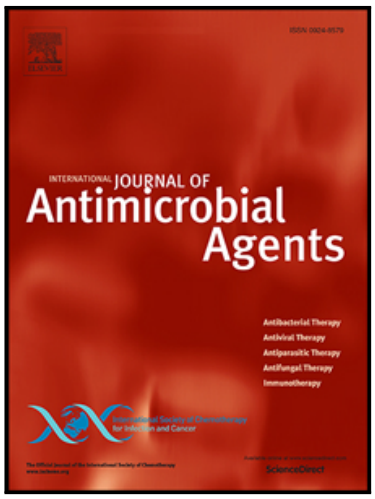

Population pharmacokinetics of vancomycin in critically ill patients receiving prolonged intermittent renal replacement therapy

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Highlights

1. Vancomycin dosing in prolonged intermittent renal replacement therapy in ICU patients is highly challenging
2. Assuming a MIC of 1 mg/L, vancomycin doses of 25 mg/kg/day are suggested to achieve efficacious, whilst minimising toxic, exposures
3. Dosing of vancomycin during PIRRT needs to be significantly higher than what is required in other forms of CRRT or where there is no RRT being used
4. The large pharmacokinetic variability of vancomycin in critically ill patients means empiric dosing is difficult and TDM is still required
5. TDM is still required, perhaps more frequently as durations of PIRRT may not always be homogenous meaning that a static guideline approach to dosing is likely to be inadequate

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Population pharmacokinetics of vancomycin in critically ill patients receiving prolonged intermittent renal replacement therapy

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[9] $ÅÐÁÒÔ Í ÅÎô ÏÆ)ÎôÅÎÓÉÖÅ #ÁÔÅ - ÅÄÉÃÉÎÅ 2ÏÙÁÌ "ÒÉÓÂÁÎÅ ÁÎÄ 7 Ï Í ÅÎ (ÏÓÐÉÔÁÌ Brisbane, Queensland, Australia; [10] Department of Pharmacy, Royal Brisbane and 7 Ï Í ÅÎ (ÏÓÐÉÔÁÌ "ÒÉÓÂÁÎÅ 1ÕÅÅÎÓÌÁÎÄ ! ÕÓÔÒÁÌÉÁ [11] Centre for Translational Anti-infective Pharmacodynamics, School of Pharmacy, The University of Queensland, Brisbane, Queensland, Australia

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Abstract

Objectives: The aim of this study was to describe the population pharmacokinetics of vancomycin during prolonged intermittent renal replacement therapy (PIRRT) in critically ill patients with acute kidney injury.

Methods: Critically ill patients prescribed vancomycin across two sites had blood samples collected during 1-3 dosing intervals during which PIRRT was performed. Plasma samples were assayed with a validated immunoassay method. Population pharmacokinetic analysis and Monte Carlo simulations were performed using Pmetrics®. The target vancomycin exposures were an AUC_{0-24}/MIC ratio of 400 for efficacy and AUC_{0-24} 700 for toxicity.

Results: Eleven critically ill patients (7 male) were enrolled and contributed 192 plasma samples 4ÈÅ ÐÁÔÉÅÎÔÓ Í ÅÁÎ Ɱ 3$ ÁÇÅ ×ÅÉÇÈÔ ÁÎÄ " -) ×ÅÒÅ 57 ± 13 years, 98 ± 43 kg and 31 ± 9 kg/m^2, respectively. A two-compartment linear model adequately described the data. The mean ± SD population pharmacokinetic parameter estimates were PIRRT clearance (CL) 3.47 ± 1.99 L/h, non-PIRRT CL 2.15 ± 2.07 L/h, volume of distribution of the central compartment (Vc) 41.85 ± 24.33 L, distribution rate constant from central to peripheral compartment 5.97 ± 7.93 h^{-1} and from peripheral to central compartment 5.29 ± 6.65 h^{-1}. Assuming a MIC of 1 mg/L, vancomycin doses of 25 mg/kg/day are suggested to achieve efficacious, whilst minimising toxic, exposures.

Conclusions: This is the first population pharmacokinetic study of vancomycin in patients receiving PIRRT and we observed large pharmacokinetic variability. Empirically, weight-based doses that are appropriate for the duration of PIRRT should be selected and supplemented with therapeutic drug monitoring.

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1. Introduction

Worldwide, approximately 2 million people die each year from acute kidney injury (AKI) [1]. In critically ill patients, sepsis is the most common cause [2]. Despite the availability of renal replacement therapy (RRT), critically ill patients with AKI still have mortality rates ranging from 40-60% [3] and no effective treatment currently exists to minimise this significant burden [1]. Approximately 5% of critically ill patients with AKI go on to require RRT [4, 5].

Prolonged intermittent renal replacement therapy (PIRRT), uses haemodiafiltration or dialysis for a 6- to 12- hour treatment duration depending on the needs of the patient. PIRRT retains the benefits of intermittent haemodialysis such as faster flow rates whilst still conferring the haemodynamic stability associated with continuous RRT [6]. Haemodiafiltration offers the highest solute flux per membrane surface area for all solutes, meaning that drug clearance is likely to be high with this RRT modality [7].

Alterations in the pharmacokinetics of antibacterials can affect the likelihood of attaining therapeutic exposures, also described as pharmacodynamic targets. This appears to be particularly common in critically ill patients receiving hydrophilic antibiotics such as vancomycin [8]. Vancomycin pharmacokinetics appear to be significantly affected by forms of RRT, like PIRRT [9].

Vancomycin is active against Gram positive bacteria including methicillin-susceptible and resistant *Staphylococcus aureus* as well as *Staphylococcus epidermidis* and streptococci. Gram positive bacteria commonly cause sepsis [10], and as such vancomycin remains an important antibacterial agent in this patient population. From a

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the area under the concentration time curve within a 24-hour period (AUC_{0-24}) to MIC ratio (AUC_{0-24}/MIC) [11]. Knowledge of the pharmacokinetics caused by PIRRT, is essential for understanding likely altered dosing needs that can consistently achieve this pharmacodynamic target.

The aim of this study was to describe the population pharmacokinetics of vancomycin during PIRRT in critically ill patients with AKI and to analyse the probability of attaining established pharmacodynamic targets.

2. Methods

2.1 Setting

This was an observational pharmacokinetic study at two intensive care units (ICU), the Gold Coast University Hospital, Australia and Hannover Medical School, Hannover, Germany. The data from Hannover Medical School had been previously published as a non-compartmental pharmacokinetic analysis [9]. Ethical approval was obtained from the local institutional Human Research Ethics Committees to conduct the study. Written informed consent was obtained from all participants or from their substitute decision-makers.

2.2 Study population

4ÈÅ ÉÎÃÌÕÓÉÏÎ ÃÒÉÔÅÒÉÁ ÆÏÒ ÔÈÉÓ ÓÔÕÄÙ ×ÅÒÅ¿ ¡ÉÇ ÁÇÅ Ï ρψ ÙÅÁÒÓ¡ ¡ÉÉÇ ÁÄ Í ÉÓÓÉÏÎ ÔÏ ÁÎ intensive care unit; (iii) clinical indication for vancomycin; and (iv) receiving PIRRT. The exclusion criteria were: (i) pregnant women; (ii) patients with active bleeding; or (iii) patients with HIV or hepatitis.

2.3 Study protocol

Vancomycin was administered at the direction of the treating physician. The timing of blood sampling to determine plasma vancomycin concentrations was different at the participating institutions.

At Gold Coast University Hospital, blood sampling occurred via an *in situ* arterial line before the drug administration (T0) and at 15 minutes (T15), T30, T60, T120, T180, T300, T480 and at T600. Further arterial blood samples were collected from each patient to establish plasma concentrations between PIRRT sessions. Sampling occurred during the first dosing period and at subsequent dosing intervals where possible thereafter. PIRRT was commenced at the discretion of the clinician and did not uniformly correspond with timing of vancomycin dosing. However, actual PIRRT times were used in the pharmacokinetic analysis. PIRRT was performed in all patients with a 4008S hemodialysis machine (Fresenius Medical Care, Bad Homburg, Germany) using Fresenius AV600S filters (surface area, 1.4 m^2; Fresenius Medical Care). For each patient, a central vein was cannulated with a standard dialysis vascular catheter. A standardized prescription consisted of hemodiafiltration with a target duration of 10 h (with 300 ml/min of blood and dialysate flow and 50 ml/min of predilution).

At the Medical School Hannover, vancomycin was administered 12 hours before PIRRT was started. On one sampling occasion, blood samples were drawn from an arterial line before administration of vancomycin and at 0.5, 1, 2, 4, 6, 8, and 12 hours after administration; before PIRRT; during PIRRT at time points 2, 4, and 6 hours; and at 0.5, 1, 3, and 8 hours after PIRRT [9]. PIRRT was performed in all patients with a batch dialysis system (GENIUS, Fresenius Medical Care, Bad Homburg, Germany) with a polysulphone high-flux dialyzer (F60S [surface area, 1.3 m2], Fresenius Medical Care. In this form of PIRRT, sterile bicarbonate dialysate is filled into the 75-L tank and is thereafter circulated in a closed-loop circuit. During PIRRT, fresh dialysate is taken from

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the top of the tank while the spent dialysate flows back to the bottom. The targeted mean blood and countercurrent dialysate flow was 160 mL/min.

Other clinical and demographic data were collected on the day of plasma sampling, including: age, sex, total body weight (TBW), and body mass index (BMI). Serum albumin and creatinine concentrations (Scr) were also collected.

2.4 Sample handling, storage and assay

Three (3) ml blood samples were placed in an ice bath immediately and centrifuged at 3000 rpm for 10 minutes. Plasma samples were stored at -80°C until bio-analysis. Vancomycin was measured in a monoclonal fluorescence polarization immunoassay (Abbott Laboratories, Abbott Park, IL).

2.5 Population pharmacokinetic modelling

To describe total vancomycin concentrations, one and two-compartment models were developed with the Nonparametric Adaptive Grid (NPAG) algorithm within the Pmetrics software package for R (Los Angeles, CA, version 1.5.1)[12, 13]. Elimination from the central compartment and intercompartmental distribution into the peripheral compartment (two compartment model) were modelled as first-order processes.

2.5.1 Population pharmacokinetic covariate screening

Age, gender, body weight and presence of RRT were evaluated as clinically relevant and physiologically plausible covariates. Covariates selection was performed using a stepwise linear regression from R on all covariates and Bayesian posterior parameters. Potential covariates were separately entered into the model and statistically tested by

use of the log-likelihood values. If inclusion of the covariate resulted in a statistically significant improvement in the log-likelihood values ($p<0.05$) and/or improved the goodness-of-fit plots, then the covariate was retained in the final model.

2.5.2 Model Diagnostics

Goodness of fit was assessed by linear regression, with an observed-predicted (both population- and individual-predicted concentrations) plot, coefficients of determination, and log-likelihood values. Predictive performance was based on mean prediction error (bias) and the mean bias-adjusted squared prediction error (imprecision) of the population and individual prediction models. The internal validity of the population pharmacokinetic model was assessed by the bootstrap resampling method (n=1000) and normalised prediction distribution errors (NPDE) [14]. Using the visual predictive check (VPC) method, parameters obtained from the bootstrap method were plotted with the observed concentrations. NPDE plots were checked for normal distribution characteristics and trends in the data errors.

2.5.3 Dosing simulations

Monte Carlo simulations (n=1000) were employed using Pmetrics to determine the probability of target attainment (PTA) of achieving the predefined AUC_{0-24}/MIC target of 400 [15] and a target of AUC_{0-24}>700 mg.h/L, which is the AUC breakpoint associated with an increased risk of nephrotoxicity [16], for varying MIC (0.5-4 mg/L) on a critically ill patient during the first 24 hours of treatment. *A priori* we considered a dosing regimen achieving 90% PTA to be sufficient. Where this criteria was not met, a balance between achieving a therapeutic and a non-toxic exposure was made to recommend a dose. The comparison of simulated probability of efficacy and toxicity for

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varied doses of 10, 15, 20, 25, 30 and 35 mg/kg 12-hourly; 10, 15, 20, 25, 30 and 35 mg/kg 24-hourly were performed for a typical 80 kg critically ill patient with AKI receiving PIRRT treatment (starting 6 hours after vancomycin administration) or receiving no PIRRT. A PIRRT duration of 12-hours was simulated to reflect a worst case scenario, where a high clearance of vancomycin could be expected. Doses were simulated for administration at a rate of 1000 mg per hour.

3. Results

3.1 Demographic and clinical data

Eleven critically ill patients (7 male) were enrolled in the study (Hannover Medical School n=8; Gold Coast University Hospital n=3). In total 192 blood samples were collected over 1-3 sampling intervals. The demographic characteristics of the patients are shown in Table 1. The mean duration of PIRRT was 6 hours for the patients at the Gold Coast Hospital and 8 hours for the patients at the Medical School Hannover.

3.2 Pharmacokinetic model building

Vancomycin pharmacokinetics was best described using a two-compartment linear model. The goodness of fit model was improved by inclusion of parameter estimates for clearance in the presence of PIRRT (CL_{PIRRT}) and the absence of PIRRT ($CL_{non\text{-}PIRRT}$). Addition of this covariate, but not others, resulted in a statistically significant improvement in the log-likelihood from the previous model (P <0.05). The addition of this covariate improved the agreement between the observed and population-predicted concentrations as well as distribution of observed data within the visual predictive check and so was retained in the final model.

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The final covariate model was as follows:

$$CL_0 = CL_{PIRRT} * PIRRT + CL_{non\text{-}PIRRT}$$

where CL_0 is the typical value of vancomycin CL, $CL_{non\text{-}PIRRT}$ is the population parameter estimate of vancomycin CL without PIRRT; CL_{PIRRT} is the population parameter estimate of vancomycin CL with PIRRT. The term PIRRT is one when PIRRT is on, and is zero when PIRRT is off.

The mean ± SD population PK parameter estimates from the final covariate model are shown in Table 2. The diagnostic plots confirm the appropriateness of the final covariate model as shown in Figure 1.

3.3 Dosing simulations

Table 3 describes the probability of target attainment for efficacy ($AUC_{0\text{-}24}$/MIC > 400) and toxicity ($AUC_{0\text{-}24}$ >700 mg.h/L) for various dosing regimens for a 24-hour period against MIC 0.5-4 mg/L for an 80 kg critically ill patient with AKI receiving a 12-hour PIRRT treatment or receiving no PIRRT. Figure 2 graphically presents the probability of target attainment data for efficacy and toxicity for a MIC of 1 mg/L. These data show that increasing doses increase the likelihood of achieving the efficacy and toxicity targets and that depending on the scenario in terms of pathogen MIC and use of PIRRT, that dosing regimens can be selected based on the highest level of efficacy and lowest level of toxicity. No dosing regimen was able to achieve the *a priori* 90% PTA for efficacy with an acceptable risk of toxicity. Assuming an MIC of 1 mg/L and in the presence of a 12-hour PIRRT treatment, a regimen of 25 mg/kg/day was associated with 72%

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likelihood of an AUC_{0-24}/MIC > 400 and a 38% likelihood of an AUC_{0-24} >700 mg.h/L which on balance was considered to be an acceptable regimen for the first 24-hours of treatment.

4. Discussion

4.1 Key findings

This is the first population PK study of vancomycin in critically ill patients undergoing PIRRT. We found that vancomycin was eliminated by PIRRT with a PIRRT clearance of 3.47 L/h, which is higher than those reported by other authors describing the PK of vancomycin in critically ill patients undergoing continuous renal replacement therapy (CRRT) 0.3 to 1.8 L/h[17, 18]. The high clearance we describe confirms the importance of selecting doses specific for PIRRT therapies rather than using data from continuous RRT therapies. We also observed high variability in pharmacokinetics (Table 2) which further emphasises the challenges of using a fixed dosing approach for a drug with a narrow therapeutic index like vancomycin and that therapeutic drug monitoring (TDM) will remain an important intervention to further optimise dosing of vancomycin in ÐÁÔÉÅÎÔïÓ ÕÎÄÅÒÇÏÉÎÇ 0)224. Our pharmacokinetic simulations suggest that vancomycin doses of 25 mg/kg/day should be most appropriate for patients receiving a 12-hour PIRRT treatment when considering achievement of therapeutic exposures and minimising the likelihood of toxic exposures. Indeed, we observed little difference in achievement of therapeutic exposures between 12- and 24-hourly administration of the same daily dose suggesting that frequency of vancomycin dosing does not significantly affect the AUC_{0-24}/MIC.

4.2 Relationship with previous papers

Despite the extensive use of vancomycin there is a dearth of information characterising its altered pharmacokinetics in patients receiving different forms of RRT in the ICU. Jamal *et al* performed a meta-review of the effect of various RRT settings on the clearance of meropenem, piperacillin and vancomycin and described the likely high clearances of vancomycin reported in critically ill patients undergoing hybrid RRT such as PIRRT [8]. The results of our study confirm these conclusions.

The total vancomycin clearance caused by PIRRT and non-PIRRT mechanisms described in the present study was 5.62 L/h. This value is considerably higher than the total clearance values previously reported during continuous RRT [18-20]. Petejova *et al* studied vancomycin pharmacokinetics in critically ill patients undergoing high-flux extended daily haemodialysis (blood flow rate 200 mL/min and dialysate flow rate 500 mL/min) and observed a total vancomycin clearance of 3.83 L/h and 4.12 L/h on days 1 and 2 of treatment, respectively [21]. These authors described a much lower vancomycin clearance off RRT of 0.82 L/h and 0.50 L/h on days 1 and 2 of treatment respectively, than was observed in our study, mean 2.15 L/h (median 1.16 L/h). Such differences in the mean non-PIRRT clearance may be due to higher drug clearance in a small number of patients with residual renal function. Another likely contributor to the higher non-PIRRT clearance in our study was that there was an incomplete RRT history for some patients. Whilst this does not change the total clearance value observed in the study, it may mean the differentiation between PIRRT and non-PIRRT clearance values are not completely accurate.

DelDot *et al* described the pharmacokinetics of vancomycin in 10 patients undergoing continuous veno-venous haemodiafiltration (CVVHDF) and observed a total vancomycin

clearance of 2.5 L/h (blood flow rate of 200 mL/min, dialysate flow rate of 1 L/h and predilution filtration solution flow rate of 2 L/h yielding and effluent flow of 3 L/h) [18].

Beumier *et al* described vancomycin clearance in patients undergoing CRRT (haemodiafiltration or haemofiltration) of 2.0 L/h [22]. Patients in this study were administered vancomycin by continuous infusion following a loading dose 35 mg/kg. This study noted that the two most important covariates affecting vancomycin concentrations were body weight and CRRT intensity. Similarly Udy *et al* used population PK modelling to describe vancomycin pharmacokinetics in 81 critically ill patients undergoing CRRT (blood flow rates 100-200 mL/min and total effluent rates ~20-40 mL/kg/h as a combination of ultrafiltration and dialysis). The authors described a median vancomycin clearance of 2.9 L/h [20].

In another vancomycin pharmacokinetics study using high-volume haemofiltration (HVHF; blood flow rates of 240 ± 20 mL/min and a substitution flow rate of 100 mL/kg/h), Escobar *et al* described a mean vancomycin clearance of 2.7 L/h and concluded variable and much higher than standard vancomycin doses would be required to achieve therapeutic concentrations during different HVHF settings [19].

Whilst many of the studies did not describe total vancomycin clearance (most described only RRT clearance), the variability in observed results and increasing clearance of vancomycin in patients treated with high flux RRT (3.8-4.1 L/h) and HVHF (2.7 L/h), the need to define vancomycin dosing in different RRT modalities needs to be studied to guide appropriate dosing.

4.3 Implications of study findings

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As previously demonstrated for gentamicin [23], dosing of vancomycin in critically ill patients with AKI receiving PIRRT needs to be significantly higher than what is required in other forms of CRRT or where there is no RRT being used. To ensure optimised dosing and achievement of vancomycin exposure targets associated with efficacy, and to avoid toxicity, loading doses of vancomycin (30 mg/kg) [24], coupled with appropriate maintenance doses (25-35 mg/kg 12-24-hourly depending on relative risk of efficacy and toxicity selected) based on the presence and duration of PIRRT should be used. The inherent large pharmacokinetic variability of vancomycin in critically ill patients means that we found that the highest likelihood for achieving AUC_{0-24}/MIC >400 was only 72%, given the escalating risk of achieving a toxic exposure AUC_{0-24}/MIC >700. Therefore, empiric dosing is difficult and TDM is still required, and in fact perhaps more frequently than in other settings because durations of PIRRT may not always be homogenous meaning that a static guideline approach to dosing is likely to be inadequate. Knowledge of the MIC of the pathogen will always be useful to help guide achievement of the PK/PD target, and if not known on a patient level, institutional data to support the AUC_{0-24}/MIC or trough concentration target is valuable to ensure maximally effective therapy that has least toxicity.

4.4 Study limitations

Although this study is the first population PK of vancomycin in critically ill patients undergoing PIRRT, it has some limitations we would like to declare. Firstly, the sample size is relatively small and emerges from two different centres which used slightly different settings of PIRRT and therefore, describing all possible correlations between PK parameters and covariates may not have been possible due to the sample size across the centres, although it is hoped that the findings would be more generalisable.

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Secondly, we did not measure vancomycin plasma concentrations at the site of infection which may provide better mechanistic data regarding the effectiveness of dosing. Thirdly, this study was neither designed nor powered to examine the effect of vancomycin exposure on patient outcome and larger studies are needed to explore this question further. Fourthly, we only simulated the first 24-hours of dosing and cannot recommend dosing thereafter, but this is typically guided by TDM rather than dosing algorithms. Finally, we have only simulated a limited number of clinical scenarios including only one PIRRT duration, PIRRT timing, as well as a small range of blood and dialysate flow, because we consider it too difficult to present all possible patient, treatment and dosing permutations. However, this paper is able to present the general effect of PIRRT on dosing requirements.

5. Conclusion

The results of this study suggest that empiric vancomycin doses of 25 mg/kg/day are required to achieve therapeutic exposures with a minimised risk of toxicity for patients receiving a 12-hour PIRRT treatment. TDM will continue to be an important tool for guiding dosing of vancomycin in critically ill patients amidst such variability in vancomycin pharmacokinetics in this patient population.

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Declarations

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Competing Interests: None to declare

Ethical Approval: Ethical approval was obtained from the local institutional Human Research Ethics Committees to conduct the study

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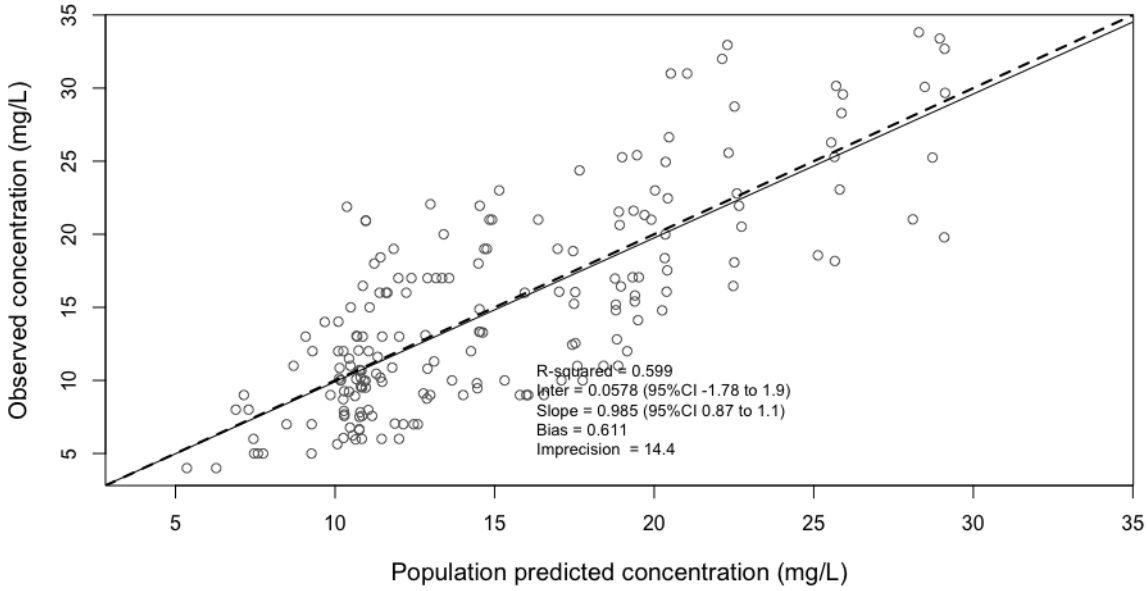
Figure 1. Diagnostic plots for the final population PK covariate model A. Population predicted concentrations (mg/L) versus observed concentrations (mg/L). The black dotted line is the line of linear regression with an R^2 value of 0.599, and the black unbroken line is the line of x equal to y. B. Individual predicted concentrations versus observed concentrations. The black dotted line is the linear regression with an R^2 value of 0.97, and the black unbroken line is the line of x equal to y; C. Visual Predictive Check of simulations of concentration (mg/L) versus time (h). Percentiles (with shaded 95% confidence intervals) are the lines shown as 95%, 75%, 50%, 25% and 5% values.

A



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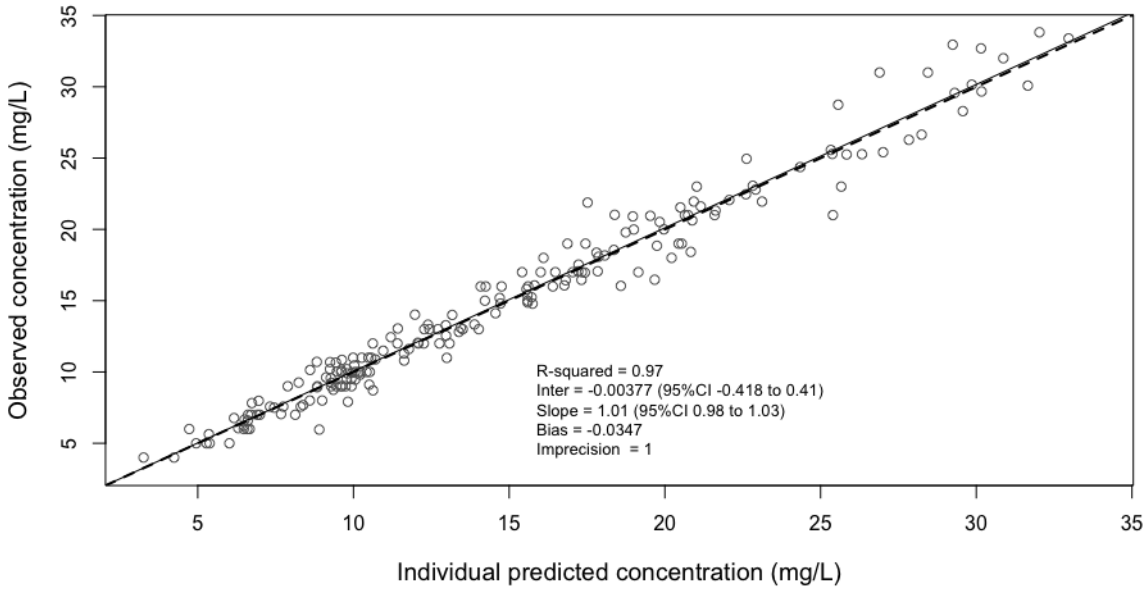


C

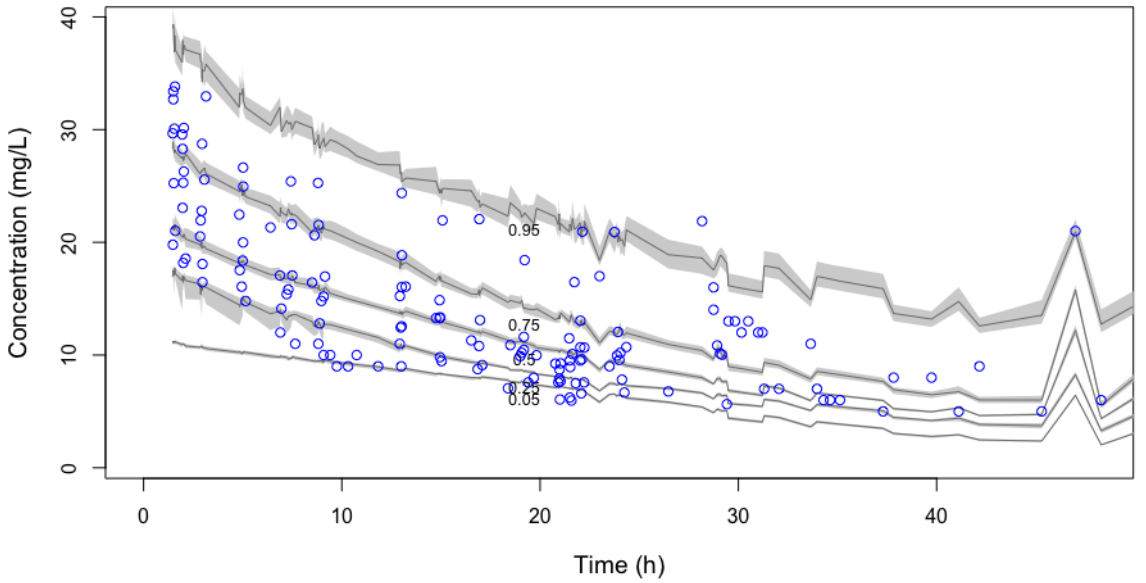
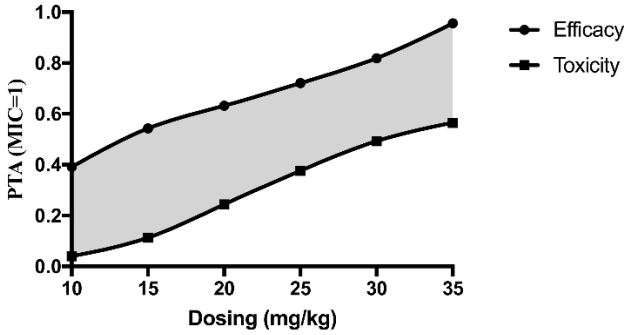


Figure 2. Probability of target attainment (PTA) for MIC 1 mg/L, where efficacy is described as $AUC_{0\text{-}24}$/MIC >400 and toxicity as an AUC >700 for various doses

administered to an 80kg critically ill patient with AKI. Graph (A) represents a 24 hour dosing schedule for a patient in which a 12-hour PIRRT treatment is given; (B) PTA represents a 12 hour dosing schedule for a patient in which a 12-hour PIRRT treatment is given; (C) represents a 24 hour dosing schedule for a patient not receiving PIRRT.

(A)



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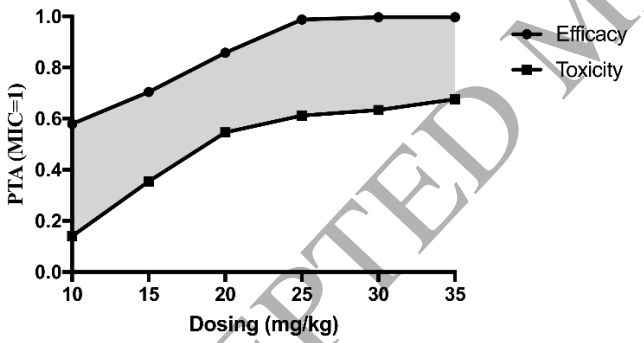

(C)

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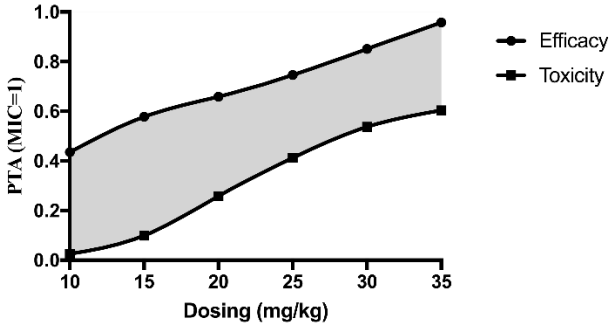

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Table 1: Demographic characteristics of included patients

Patient	Age (years)	Height (cm)	Sex (F/M)	Weight (kg)	BMI (kg/m^2)
1	74	160	F	60	23.4
2	51	158	F	50	20.0
3	66	180	M	84	25.9
4	49	189	M	80	22.4
5	53	165	F	80	29.4
6	53	175	M	170	55.5
7	35	180	M	118	36.4
8	65	175	M	90	29.4
9	49	187	M	182	52.0
10	79	160	M	70	27.3
11	51	180	F	90	27. 8
Median	53	175		84	27.8
Quartile 1	50	163		75	24.7
Quartile 3	65.5	180		104	32.9

BMI z body mass index

Table 2: Population pharmacokinetic parameter estimates for vancomycin in the final two compartment covariate model

	Mean	CV%	Median
CL_{PIRRT} (L/h)	3.47	57.47	3.85
$CL_{non\text{-}PIRRT}$ (L/h)	2.15	96.49	1.16
Vc (L)	41.85	58.12	26.45
k_{PC} (h^{-1})	5.29	125.65	0.32
k_{CP} (h^{-1})	5.97	132.97	0.58

CL_{PIRRT}, population clearance of vancomycin during PIRRT; $CL_{non\text{-}PIRRT}$, population clearance of vancomycin off PIRRT; Vc, population volume of distribution in the central compartment; k_{CP}, rate constant for vancomycin distribution from the central to the peripheral compartment; k_{PC}, rate constant for vancomycin distribution from the peripheral to the central compartment.

Table 3. The probability of target attainment of vancomycin using various dosing schedules over a 24-hour period including a 12-hour PIRRT treatment or without PIRRT for an 80 kg patient ($AUC_{0\text{-}24}$/MIC > 400 defines efficacy and $AUC_{0\text{-}24}$ >700 defines toxicity)

Dosing regimens	MIC (mg/L)	PIRRT		Non-PIRRT	
		Probability of target attainment			
		$AUC_{0\text{-}24}$/MIC >400	$AUC_{0\text{-}24}$ >700	$AUC_{0\text{-}24}$/MIC >400	$AUC_{0\text{-}24}$ >700
10mg/kg/24h	0.5	0.960	0.040	0.959	0.025
	1	0.391	0.040	0.435	0.025
	2	0.019	0.040	0.012	0.025
	4	0	0.040	0	0.025

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15mg/kg/24h	0.5	0.995	0.113	0.994	0.099
	1	0.543	0.113	0.578	0.099
	2	0.053	0.113	0.043	0.099
	4	0	0.113	0	0.099
20mg/kg/24h	0.5	0.996	0.244	0.999	0.258
	1	0.632	0.244	0.659	0.258
	2	0.127	0.244	0.12	0.258
	4	0	0.244	0	0.258
25mg/kg/24h	0.5	0.998	0.376	1	0.412
	1	0.721	0.376	0.746	0.412
	2	0.247	0.376	0.26	0.412
	4	0.005	0.376	0.001	0.412
30mg/kg/24h	0.5	1	0.493	1	0.537
	1	0.819	0.493	0.851	0.537
	2	0.359	0.493	0.405	0.537
	4	0.016	0.493	0.008	0.537
35mg/kg/24h	0.5	1	0.565	1	0.604
	1	0.956	0.565	0.958	0.604
	2	0.481	0.565	0.518	0.604
	4	0.027	0.565	0.018	0.604
10mg/kg/12h	0.5	0.990	0.14	0.994	0.117
	1	0.580	0.14	0.583	0.117
	2	0.075	0.14	0.058	0.117
	4	0	0.14	0	0.117
15mg/kg/12h	0.5	0.997	0.355	1	0.345
	1	0.705	0.355	0.717	0.345
	2	0.214	0.355	0.202	0.345
	4	0	0.355	0.001	0.345
20mg/kg/12h	0.5	0.999	0.546	1	0.547
	1	0.858	0.546	0.852	0.547
	2	0.42	0.546	0.411	0.547
	4	0.017	0.546	0.014	0.547
25mg/kg/12h	0.5	1	0.612	1	0.626
	1	0.988	0.612	0.986	0.626
	2	0.564	0.612	0.57	0.626
	4	0.047	0.612	0.033	0.626
30mg/kg/12h	0.5	1	0.634	1	0.655
	1	0.997	0.634	0.999	0.655
	2	0.617	0.634	0.63	0.655
	4	0.094	0.634	0.081	0.655
35mg/kg/12h	0.5	1	0.676	1	0.688
	1	0.997	0.676	1	0.688
	2	0.633	0.676	0.652	0.688
	4	0.154	0.676	0.152	0.688

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PIRRT ≙ prolonged intermittent renal replacement therapy; AUC_{0-24} ≙ area under the concentration-time curve from 0-24 hours; MIC ≙ minimum inhibitory concentration;

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