

The Pharmacokinetics, Optimal Dose and Therapeutic Monitoring of Vancomycin in Severe Burn Patients

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Abstract

Objectives: This paper investigated the pharmacokinetic (PK) change, optimal dose and therapeutic monitoring method of vancomycin in severe burns.

Method: This is a retrospective, matched cohort study. Nine burn patients were included, and each individual was matched with a control critically ill patient. Vancomycin concentrations were analyzed using the first order pharmacokinetic principles to calculate elimination rate constant (K), half-life ($t_{1/2}$), volume distribution (V_d), total body clearance ($CL_{\text{vancomycin}}$) and the 24-hour area under the curve (AUC_{24h}). Population PK analysis and Monte Carlo simulation was used to investigate optimal dose.

Results: The mean burn area of the burn group and age was 60% and 20 years-old respectively. The loading dose and daily maintenance dose was significantly higher in burn group than that in control group. Vancomycin clearance was significantly higher ($p < 0.05$) in burns patients when compared to control patients. CL_{Cr} (creatinine clearance) was not significantly correlated to $CL_{\text{vancomycin}}$ (vancomycin clearance) in both groups. C_{trough} (serum trough concentration) was significantly correlated with AUC_{24h} in the control group ($r = 0.98$, $R^2 = 0.96$, $p < 0.01$), but not in the burn group ($r = 0.63$, $R^2 = 0.40$, $P = 0.07$). Daily dose of 5000 mg of vancomycin could achieve 90% probability of target attainment if target was AUC_{24h}/MIC (minimum inhibitory concentration) > 400 .

Conclusion: Two steady state concentrations but not C_{trough} is an appropriate reference for vancomycin therapeutic monitoring. A daily dose of at least 5000 mg is suggested in severe burn patients with normal renal function ($CL_{Cr} > 90$ mL/min).

Keywords: Burns; Vancomycin; Pharmacokinetics; Optimal dose, Therapeutic drug monitoring

Introduction

Vancomycin, a potential nephrotoxic antibiotic, is commonly used in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection or sepsis. The antibiotic is excreted by kidney and 55% of it is bound to albumin [1]. However, the pharmacokinetics (PK) is significantly altered in severe burn patients [2,3]. Previous studies have shown that the renal clearance and volume distribution (V_d) of vancomycin in burn patients is higher than it is in controls, while the half-life is shorter [4-6]. Thus, larger loading and the use of more frequent dosing of vancomycin especially when intermittent dosing is used are needed to maintain therapeutic serum level, and inadequate dosing is not an uncommon clinical problem [7].

To monitor clinical efficacy, the 24 h area under the serum concentration-time curve to minimum inhibitory concentration ratio ($AUC_{24h} : MIC$) of > 400 has been suggested as a standard clinical reference for vancomycin dosing [8]. As C_{trough} significantly correlates with the AUC_{24h} , a C_{trough} level of 15–20 mg/L is recommended to achieve an AUC_{24h} / MIC of 400 if the MIC is 1 mg/L. However, its use as reference for dosage adjustment in severe burn patients has been questioned as the correlation of C_{trough} with AUC_{24h} remains debatable in this special group [9,10].

The main purpose of this retrospective study was to investigate the correlation of C_{trough} with AUC_{24h} in severe burn patients. The burn patients in similar ages and injury mechanism from the 2015 Taiwan cornstarch dust explosion have provided a clinical model with least

spatial and temporal effect. Another aim of this study was to define the optimal dose for this population to achieve $AUC_{24h} / MIC > 400$. The study obtained approval from The NTUH Ethics Committee (NTUH-201508031DINA).

Methods

This is a retrospective chart review study. Thirty-three adult burn patients (> 18 years old) admitted to the National Taiwan University Burn centre following the color cornstarch powder explosion in a water park on June 28, 2015 were reviewed. Only those who received vancomycin therapy at least for 2 days after burn injury with peak (C_{peak}) and trough (C_{trough}) serum concentrations available were included in the study.

Patient demographic data including age, sex, height, weight, total

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body surface area of burn (%), timing of vancomycin infusion (day after burn injury), S_{Cr} (serum creatinine), albumin, indications, loading dose, maintenance dose, dosing interval, infusion time and serum concentration were collected. Weight and S_{Cr} were recorded on the day of blood sampling for serum concentration.

The dose and dosing interval were decided by attending physicians or clinical pharmacists, and the infusion time of vancomycin was 1 hour for dose lower than or equals to 500 mg, and 2 hours for dose between 500 to 1000 mg and so on. The C_{peak} C_{trough} were followed at 2 hours after the end of vancomycin infusion, and within 1 hour before vancomycin infusion. Both were followed after at least 5 doses of vancomycin. Vancomycin concentrations were analyzed by using first order pharmacokinetic principles (Sawchuk and Zaske method) to calculate PK parameters such as elimination rate constant (K), half-life ($t_{1/2}$), V_d , total body clearance ($CL_{vancomycin}$) and AUC_{24h} [11]. The formula was shown as follows:

$$K (hr^{-1}) = \ln (Cp2 / Cp1) / t, (Cp1 \text{ and } Cp2)$$

stands for two serum concentration in different time at steady state,
 $t = \text{time difference between } Cp1 \text{ and } Cp2$

$$t1/2 (hr) = 0.693 / K$$

$$Vd (L) = [Dose * (1 - exp - k * tin) * exp - k * (\tau - tin)] / [tin * Ctrough * k * (1 - exp - k * \tau)]$$

(τ : dosing interval, t_{in} : infusion time C_{trough} : serum trough concentration)

$$CL (L / hr) = Vd * K$$

$$AUC_{24h} (mg * hr / L) = \text{Daily dose} / CL$$

For each patient in the burn group, a control subject in intensive care unit was matched by creatinine clearance (CL_{Cr} , mL/min). Matching was based on CL_{Cr} value with a difference of <30 mL/min between matched pair, or on different stages of chronic kidney disease with a range of CL_{Cr} value between groups (> 90, 60-89, 30-59, <30 mL/min) [12]. The CL_{Cr} was estimated by the Cockcroft and Gault (CG) method [13]. If patient's S_{Cr} was lower than 1.0 mg/dL, it will be replaced by 1.0 mg/dL for better estimate of patient's renal function in intensive care unit [14]. For obese patients [$(\text{true body weight} - \text{ideal body weight}) / \text{ideal body weight} > 30\%$]

the ideal body weight was used to estimate the CL_{Cr} .

The vancomycin serum concentrations were measured by a fluorescence polarisation immunoassay (AxSYM system, Abbott Laboratories, Abbott Park, Illinois, USA). The sensitivity of the assay (the lowest measurable level) was 2 mg/L, and the coefficients of variation at 7.0, 35.0 and 75.0 mg/L were all less than 5%.

For optimal vancomycin dose investigation, the population pharmacokinetics analysis was performed for burn patients by NONMEM version 7.2 (ICON Development Solutions, Ellicott City, MD, USA) with G77 FORTRAN compiler. Both one and two-compartment structural models were tested using the first-order conditional method of estimation (FOCE). Clearance and volume of distribution were estimated. A proportional error model was used to characterize the inter-individual variability (% CV) of each parameter. Different residual error models (i.e., additive, proportional and combined additive and proportional) were examined in order to find the better error model to characterize the unexplained residual variability. Due to the limited sample size (n=9), no attempts were made to identify the potential influential covariates.

The final model was assessed by visual inspection of the following diagnostic plots: (a) observed concentrations vs. individual predicted concentrations; (b) observed concentrations vs. predicted concentrations; (c) conditional weighted residuals (CWRES) vs. time and (d) absolute individual weighted residuals (IWRES) vs. individual predictions. A bootstrap resampling technique with 200 replications was conducted to evaluate the stability of the final model using Wings for NONMEM (WFN; Version 6.1, University of Auckland, New Zealand). The final model estimates were compared to the median and the 2.5th and the 97.5th percentiles of the parameter estimate obtained from successfully converged bootstrapping runs. The final population PK model was used for simulations to investigate the probability of target attainment (PTA) for different daily dose (2000 mg to 6000 mg). The pharmacodynamic target attainment was defined as achieving $AUC_{24h} / MIC \geq 400$, and the MIC range values were 0.125, 0.25, 0.5, 1.0 and 2.0 mg/L [8]. For each dose examined, 5,000 burn patients were simulated using Monte Carlo simulation in NONMEM and the percentage of patients exceeding an AUC_{24h} / MIC of 400 was computed.

Continuous data were summarized as mean with standard deviation. The demographic and PK data were compared by a two-tailed paired *t* test. Simple linear regression analysis was used to test the correlation between variables. A *p*-value of 0.05 or lower was considered statistically significant. The statistical analysis was performed using SPSS 11.5 (SPSS Inc, Chicago, Illinois, USA).

Results

Nine young adult burn patients were included in this study, and each individual was matched with a non-burn critical ill patient (control group). The mean surface area of second- and third-degree burn was 60% TBSA (total body surface area). There were no significant differences between the 2 groups in the demographic data except age and albumin (Table 1). Patients with burn injury were younger than the non-burn group (20.78 vs. 33.89 years-old) and had lower albumin level (2.6 vs. 3.1 g/dL). All patients in the burn group received vancomycin for the treatment of MRSA empirically. Vancomycin was given before the 10th day after burn except 1 started on 27th day. The indications of vancomycin for the non-burn group were MRSA related bacteremia, pneumonia and wound infection in 3 patients respectively, and empirical use for the others.

In the burn group, the loading dose and daily maintenance dose was 25.42 ± 4.53 mg/kg and 45.03 ± 10.43 mg/kg/day respectively, which was significantly higher than that of non-burn group (14.46 ± 1.40 mg/kg and 30.53 ± 12.86 mg/kg/day) (Table 2). The vancomycin clearance was significantly higher in the burn group than that in the non-burn (10.66 L/hr \pm 3.28 vs. 6.85 L/hr \pm 3.54), corresponding to a 55% higher CL in burn patients ($p < 0.05$). Similarly, the trend of K and V_d , was higher in the burn group than the non-burn although it was statistically insignificant. CL_{Cr} was not significantly correlated with vancomycin CL in both groups ($r = 0.13$, $R^2 = 0.02$, $P = 0.74$ in burn group vs. $r = 0.59$, $R^2 = 0.35$, $P = 0.09$ in non-burn group) (Figure 1). C_{trough} was not significantly correlated with AUC_{24h} in the burn group ($r = 0.63$, $R^2 = 0.40$, $P = 0.07$), but was correlated significantly in the non-burn group ($r = 0.98$, $R^2 = 0.96$, $p < 0.01$) (Figure 2).

A one-compartment model with first-order elimination adequately characterized the observed concentration time profiles of vancomycin in burn patients. The final population pharmacokinetic model resulted in a clearance of 9.56 L/hr with an inter-individual variability of 17.3%. Volume of distribution is determined to be 50 L with an inter-

Patient No. ^a	Age (yr)	Sex ^b	Ht (cm)	Wt (kg)	S _{cr} (μmol/L)	CL _{cr} (mL/min)	Albumin (g/dL)	TBSA burned ^c (%)	Vancomycin initiation time after burn injury (days)	
B1	18	F	158	64.8	35.4	93.33	2.8	60		6
B2	21	F	167	69	35.4	96.9	3.6	60		10
B3	23	F	158	62.7	35.4	86.6	2.3	60		6
B4	21	F	160	64.1	35.4	90.05	2.8	50		6
B5	20	M	175	78.5	53.0	130.8	2.8	50		6
B6	24	F	160	97 [#]	70.7	73.95	2.2	50		9
B7	20	M	160	68.8	53.0	114.7	2.2	50		6
B8	20	M	175	76.6	53.0	127.7	2.6	80		6
B9	20	M	175	58	44.2	96.67	2.5	70		27
Mean (SD)	20.78[†] (1.79)		165.33 (7.71)	71.06 (11.71)	46.2 (12.3)	101.19 (19.18)	2.6[†] (0.4)	60 (11)		9 (7)
C1	38	F	160	63.6	53.0	76.58	3.4			
C2	18	M	176	85.8	150.3	85.51	3.8			
C3	40	F	160	60.5	26.5	71.42	2.8			
C4	38	M	170	53.9	53.0	76.36	2.8			
C5	18	M	170	69.8	26.5	118.27	3.6			
C6	44	M	173	52.6	61.9	70.13	2.2			
C7	42	M	156	68	70.7	92.55	3.0			
C8	35	M	171	68.3	61.9	99.6	3.3			
C9	32	M	161	76.4 [#]	97.2	85.05	2.9			
Mean (SD)	33.89 (9.68)		166.33 (7.09)	66.54 (10.51)	66.8 (38.1)	86.16 (15.48)	3.1 (0.5)			

^aB: Burn group; C: Matched cohort, ^bM: Male; F: Female, ^cTBSA: Total body surface area of second and third degree burn
[#] obese * *p*<0.05 compared to control group

Table 1: Demographic data in the burn and matched control groups.

Patient No. ^a	LD ^a (mg/kg)	MD ^b (mg)	DI ^c (hr)	Daily dose (mg/kg/day)	Time of TDM ^d (days)	C _{peak} ^e (mg/L)	C _{trough} ^h (mg/L)	K (hr ⁻¹)	t _{1/2} (hr)	CL (L/hr)	V _d (L/kg)	AUC _{24h} (mg*hr/L)
B1	23.15	1000	8	46.30	2	13.95	9.66	0.09	7.5	9.62	1.61	312
B2	28.99	1000	8	43.48	5	9.27	3.18	0.27	2.6	14.80	0.80	203
B3	23.92	1000	8	47.85	3	11.94	7.52	0.12	6.0	11.40	1.57	263
B4	31.2	1000	8	46.80	2	9.81	4.54	0.19	3.6	14.12	1.14	212
B5	25.48	1000	8	38.22	2	18.46	4.44	0.36	1.9	7.17	0.26	418
B6	30.93	1000	8	30.93	5	20.65	11.65	0.14	4.8	6.63	0.48	453
B7	21.8	1000	8	43.60	2	12.78	9.55	0.07	9.5	10.42	2.07	288
B8	26.11	1000	8	39.16	2	9.38	5.54	0.13	5.3	14.58	1.44	206
B9	17.24	1000	6	68.97	1	20.56	10.64	0.29	2.4	7.24	0.43	553
Mean (SD)	25.42[†] (4.53)	--	--	45.03[†] (10.43)	--	14.09 (4.66)	7.41 (3.09)	0.18 (0.10)	4.8 (2.5)	10.66[†] (3.28)	1.09 (0.63)	323 (124)
C1	15.00	500	6	31.44	2	8.31	3.66	0.27	2.6	10.21	0.59	196
C2	11.65	1000	24	11.65	3	19.04	4.98	0.07	10.3	3.60	0.63	278
C3	15.00	500	6	33.06	1	10.95	7.56	0.12	5.6	7.89	1.06	254
C4	16.69	1000	12	37.25	5	31.10	21.1	0.05	14.4	3.03	1.17	664
C5	14.32	500	6	28.65	5	7.77	3.13	0.30	2.3	10.84	0.52	184
C6	15.00	500	8	28.51	3	25.51	20.73	0.04	16.9	2.56	1.19	585
C7	14.7	750	12	22.05	3	10.60	3.99	0.12	5.7	7.80	0.94	192
C8	14.64	1000	6	58.56	6	14.00	9.85	0.18	3.9	11.44	0.95	350
C9	13.1	600	8	23.56	6	18.34	14.64	0.06	12.4	4.27	1.00	422
Mean (SD)	14.46 (1.40)			30.53 (12.86)		16.18 (8.05)	9.66 (7.20)	0.13 (0.10)	8.2 (5.4)	6.85 (3.54)	0.89 (0.25)	347 (176)

^aLD: Loading Dose, ^bMD: Maintenance Dose, ^cDI: Dosing Interval, ^dTDM: Therapeutic Drug Monitoring, after vancomycin initiation, ^e2hr after infusion, ^hwithin 1hr before infusion

**p*<0.05 compared to control group

Table 2: Vancomycin data in the burn and matched control groups.

individual variability of 37.4% (Table 3). Residual variability was best described by an additive model and was determined to be 0.115 mg/L.

The diagnostic plots of the final model are given in Figure 3. Overall, there was a good correlation between observed and individual- and population-predicted vancomycin concentrations (Figures 3A and 3B). No obvious bias pattern was observed for the plots of CWRES

versus time (Figure 3C) and IWRES versus individual predicted concentrations (Figure 3D). From 200 bootstrap runs, 180 runs with successful minimization were included in the bootstrap analysis. All model estimates were similar between the bootstrap analysis and the final model. Overall the bootstrap analysis indicated that the final model was stable and estimated parameters were reasonably precise.

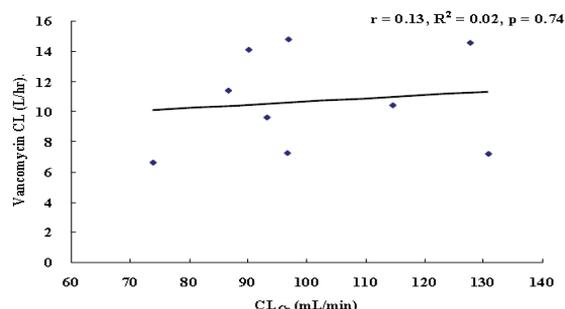


Figure 1A: Vancomycin clearance vs. creatinine clearance: Burn group.

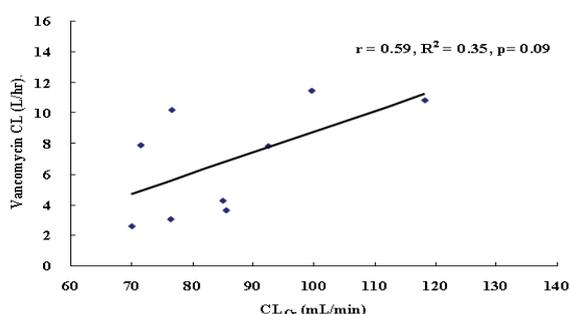


Figure 1B: Vancomycin clearance vs. creatinine clearance: Non-burn group.

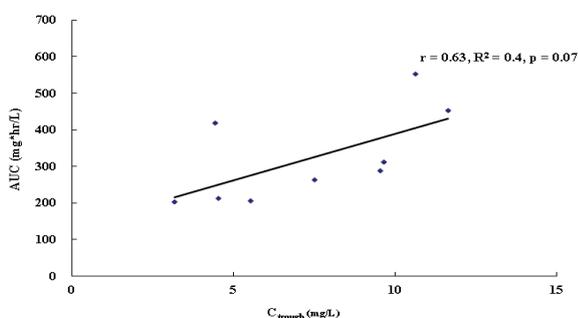


Figure 2A: Area under the curve vs. vancomycin trough concentration: Burn group.

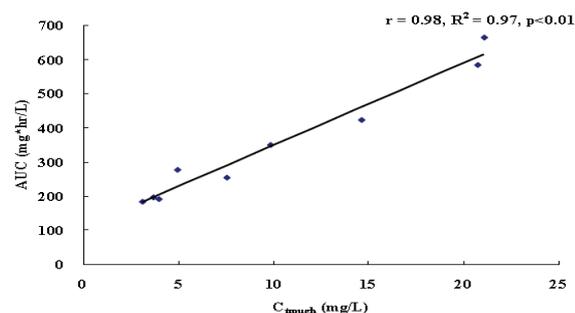


Figure 2B: Area under the curve vs. vancomycin trough concentration: Non-burn group.

Parameters (unit)	Estimate (%RSE)	200 Bootstrap Replicates Median (2.5 th , 97.5 th percentile)
Fixed parameters		
CL (L/hr)	9.56 (9.4)	9.41 (7.87, 11.3)
V _d (L)	50.0 (25.2)	48.4 (31.2, 77.9)
Interindividual variability		
ω _{CL} (%)	17.3 (37.1)	15.3 (0.2, 26.1)
ω _V (%)	37.4 (47.5)	30.7 (0.2, 58.9)
Residual variability		
σ (mg/L)	0.115 (39.5)	0.111 (0.039, 0.16)

CL: Clearance, V_d: Volume of Distribution, RSE: Relative Standard Errors
ω: Inter-subject variability, σ: Residual variability

Table 3: Pharmacokinetic parameters in burn group by population pharmacokinetic analysis.

The PTA ($AUC_{24h}/MIC > 400$) for different daily dose of vancomycin by MIC was presented in Figure 4. Based on the simulation results, it was observed that daily dose greater than 3000 and 5000 mg yielded PTA > 90% against MIC of ≤ 0.5 and ≤ 1.0 mg/L, respectively. However, at a MIC of 2.0 mg/L, even though increasing the daily dose up to 6000 mg only provided a PTA of 10%.

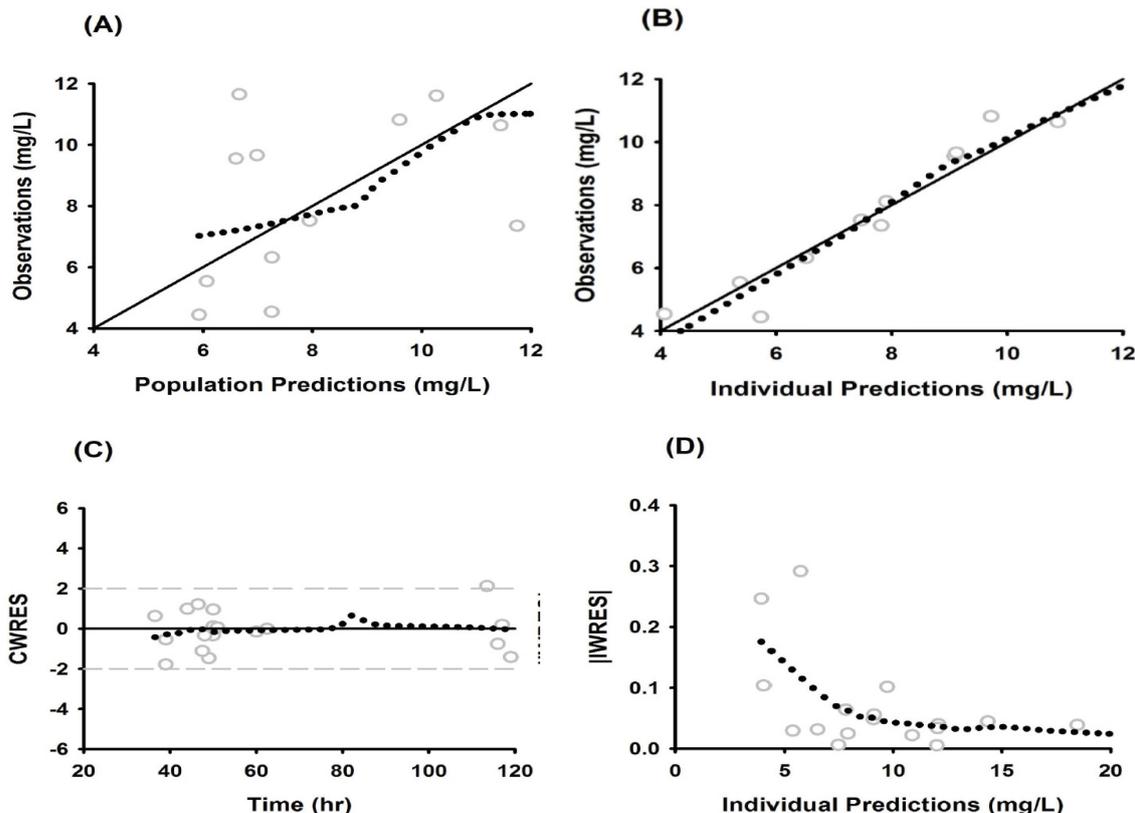
Discussion

MRSA infection or sepsis is a life-threatening clinical problem commonly encountered in severe burns. A potential nephrotoxic antibiotic, vancomycin, is usually the treatment of choice. The outcome is associated with proper antibiotic dosing. Inadequate doses will lead to suboptimal bactericidal activities leading to mortality or the development of resistance, while overdoses will cause nephrotoxicity. C_{trough} of 15-20 mg/L and $AUC_{24h}/MIC > 400$ have been recommended.

As in other studies in the literature, this study has shown that the clearance of vancomycin is augmented in severe burn injury [4-6]. The results provide an explanation for the observation that although burn patients received higher loading and maintenance dose of vancomycin, the C_{trough} was not significantly higher than that in the non-burn group. Increased glomerular filtration rate, extensive loss through burn wounds, and decreased or altered serum binding proteins are possible explanations for the enhanced vancomycin elimination noted in the burn patients [2]. A study of serum protein-binding characteristic of vancomycin has shown that vancomycin preferentially binds to albumin and immunoglobulin A (IgA), the serum level of which was found to decrease 2 days after burns (< 0.001) [15]. Consequently, it leads to increased elimination due to less protein binding. Our data was compatible with this finding by lower albumin level and higher vancomycin clearance in burn group.

Besides higher clearance in the burn group, the V_d is also higher in the burn group. This could be attributed to more aggressive resuscitation in the burn group than that in the non-burn group. According to Parkland formula, the total amount of resuscitation fluids for burn group was around 14.4 liter (TBSA (%) × body weight × 4 mL), while only around 2 liter (30 mL/kg) was given for non-burn group based on the recommendation of fluid resuscitation in sepsis patients [16,17]. This also further explains why the C_{trough} was not significantly higher in the burn group than that in the non-burn group although larger dose was administered to burn group.

Our results have shown that C_{trough} was not correlated well to AUC_{24h} in burns patients than that in control patients. The result is compatible to the statements by Michael N. Neely who said that the traditional approach to therapeutic drug monitoring (TDM) by comparing the



Note: Solid and dotted line: the line of identity and LOESS smoothed fit, respectively.

Figure 3: Basic goodness-of-fit plots for the final population pharmacokinetic model
 (A) Observations vs. population predictions.
 (B) Observations vs. individual predictions.
 (C) Conditional weighted residuals (CWRES) vs. time.
 (D) Absolute individual weighted residuals (IWRES) vs. individual predictions.

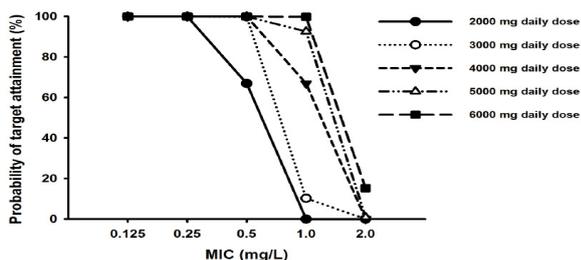


Figure 4: Probability of target attainment of $AUC_{24h}/MIC > 400$ for 5000 simulated burn subjects following different daily doses of vancomycin.

C_{trough} to a predefined range is a very poor surrogate for estimation of the AUC and overall vancomycin exposure [9]. He emphasized that C_{trough} will underestimate the true AUC_{24h} by about 25%. However, on the other hand, our study also has shown that C_{trough} was significantly correlated with AUC_{24h} in the non-burn patient group. These findings are compatible to IDSA guidelines, which stated that C_{trough} is a tool to monitor the therapeutic level and toxicity of vancomycin due to its good correlation to AUC_{24h} in the general population [1]. In fact, the association between C_{trough} and AUC_{24h} may be explained by the pathophysiological changes in burns. Following the ebb phase of early

severe burn injury, more aggressive fluid resuscitation than that in control group results in higher than normal cardiac output and greater blood perfusion to the liver and kidneys, consequently increases vancomycin clearance and V_d [2]. Besides, there is tremendous interpatient or inpatient variability, especially in burns of different stages. These factors may explain why C_{trough} may not be an appropriate reference to assess the optimal therapeutic vancomycin level in burns.

Some studies showed that the correlation between C_{trough} and the actual AUC_{24h} were subjected to individual variations such as dosing interval and infusion time [9,10]. Again, these findings were against the approach to use C_{trough} alone as a reference. C_{trough} would be proportional to AUC_{24h} only under the situation of fixing dosing interval and infusion time. In burn patients, higher dose of vancomycin is needed and this makes fixing infusion time difficult due to the concern of red man syndrome [18]. This further ensures the necessity of estimate of AUC_{24h} by at least 2 points of serum concentration, instead of C_{trough} alone.

As C_{trough} does not correlate to AUC_{24h} well in severe burns patients, two points of serum concentration were suggested in our study for the mathematical derivation of PK parameters and AUC_{24h} , which are beneficial in vancomycin serum level monitoring and dose adjustment in severe burns [19]. Because of increasing CL and V_d in severe burn patients, the optimal dose of vancomycin in this population would be

higher than that in general population. If vancomycin MIC of MRSA was 1 mg/L, 5000 mg of vancomycin daily was needed to have the better chance to achieve the target of $AUC_{24h}/MIC > 400$ in this study. Because of vancomycin MIC creep in MRSA and a high percentage of vancomycin MIC being 1 mg/L, the initial vancomycin dosing of 5000 mg should be given in severe burn patients with normal renal function ($CL_{Cr} > 90$ mL/min) before confirming MIC data [20]. However, due to wide individual variations among burn patients, closed serum level monitoring is still highly recommended. As the half-life of vancomycin (4.8 ± 2.5 hours) is comparatively short in burn patients, serum concentration can be checked 1 to 2 days after initiation of vancomycin to ensure efficacy and safety.

Our results have confirmed that large burn size and initiation of vancomycin infusion within 2 weeks of burn in our study population have yielded a high value of CL and V_d . The results are compatible to the statement that burn size and timing of vancomycin infusion affect PK [5,21]. As vancomycin is mainly excreted by kidneys, previous study has shown that estimated CL_{Cr} is a good predictor of vancomycin clearance [22]. However, this is not true in our study, as forming an initial dose nomogram based on CL_{Cr} is not possible (Figure 1).

These findings are compatible to other study results stating that creatinine-based formula is a less reliable tool for therapeutic drug monitoring in severe burn patients. The complicated burn pathophysiology has shown that cystatin C-based formula, Cockcroft and Gault methods, Modification of Diet in Renal Disease (MDRD) equations and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation are imprecise and inaccurate for renal function monitoring [23,24]. Besides dehydration due to the tremendous loss of fluid, the suppressed renal function by toxic substances or the decreased renal flow, the decreased serum creatinine production due to the loss of muscle mass, the increased glomerular filtration rate due to the increased cardiac output during the hypermetabolic state, and the disturbed liver metabolism have significantly affect the reliability of CL_{Cr} measurement as a tool for antibiotic dosing. In fact, the glomerular filtration rate is overestimated by creatinine clearance in renal failure due to tubular creatinine secretion [25]. In short, the use of creatinine-based formula which is only suitable to patients with stable renal function is inappropriate in severe burn patients. However, urine collection for creatinine clearance remains the clinically gold standard for antibiotic dosing in these patients.

The main drawback of the study is quite small sample size, besides the inherent limitations of retrospective studies. The differences of vancomycin V_d between groups may be significant if the sample size is large, and multi-centre prospective study is thus indicated. Also, further studies are needed to confirm the dose recommended in this study.

Conclusion

Our results have proved that C_{trough} alone was not an appropriate reference for monitoring the therapeutic and toxic effect of vancomycin in severe burn patients due to its poor correlation with AUC_{24h} , in which two points of serum concentration are required. Creatinine clearance-based dosage formula is not feasible due to its lack of correlation with vancomycin clearance in burn patients. We suggest a daily dose of at least 5000 mg to attain an optimal therapeutic value of $AUC_{24h}/MIC > 400$ if vancomycin MIC was 1 mg/L of MRSA in severe burn patients with normal renal function.

Conflict of Interest

There was no conflict of interest in this study.

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