Contemporary Vancomycin Dosing in Chronic Hemodialysis (HD) Patients Does Not Meet AUC Targets: Development of a New Dosing Model Using Monte Carlo Simulation (MCS)

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Introduction

- Current vancomycin consensus guidelines recommend achieving trough levels of 15-20mg/L to practically attain AUC_{24h}/MICs ≥400, values known as the pharmacokinetic-pharmacodynamics (PK-PD) target. [1] However, discordance between troughs and clinical outcomes has led the new guideline writers to consider a direct AUC-based dosing approach. [2-4]
- Vancomycin is frequently used in hemodialysis (HD) patients due to prevalent methicillin resistant *Staphylococcus aureus* (MRSA) infection. However, inconsistent vancomycin dosing recommendations using a plasma trough concentration-based approach has led to increasing vancomycin resistance and infection remaining as the second leading cause of mortality in these patients. [5]
- AUC_{24h} >700-1,300 mg*h/L has been reported as the toxicity threshold associated with nephrotoxicity, but concern for nephrotoxicity is largely irrelevant for patients with ESRD, requiring maintenance HD. [2,3,6]
- No dosing studies have been conducted to attain the known PD target and to avoid the toxicity threshold in HD patients with MRSA infection.

Objective

- To evaluate the drug exposure (AUC) attained with a published HD vancomycin dosing regimens. [7]
- To determine initial vancomycin dosing attaining AUC_{24h} of 400-700 mg*h/L and to devise a therapeutic drug monitoring (TDM) - guided dosing algorithm to individualize the subsequent dosing using Monte Carlo Simulation (MCS) in HD patients.

Methods

1. Mathematical PK Model Development

- One compartment PK model with the first elimination order was structured to predict vancomycin disposition, using prior demographic, PK, and dialytic data.

Table 1. Input PK Parameters used in MCS [8-11]

Parameters	Mean ± SD [Range]
Volume of Distribution (L/kg)	0.9 ±0.27 [0.38-1.55]
Weight (kg)	75 ± 23 [40-150]
Ke_interdialytic (hr $^{-1}$)	0.0035 [0.0010-0.0061]
$t_{1/2}$ _Interdialytic (hr)	198 [113.6-693]
Ke_high-flux intradialytic (hr $^{-1}$)	0.110 [0.066-0.154]
$t_{1/2}$_high-flux intradialytic (hr)	6.3 [4.5-10.5]
Bioavailability during high-flux HD	0.74 ± 0.15 [0.56-0.84]
Ke_low-flux intradialytic (hr $^{-1}$)	0.055 [0.033-0.077]
$t_{1/2}$_low-flux intradialytic (hr)	13 [9-21]
Bioavailability during low-flux HD	0.84 ± 0.17 [0.75-1]

- Four-hour HD with either high-flux or low-flux dialyzer occurring on Monday, Wednesday and Friday was modelled. Vancomycin therapy was commenced either Monday, Wednesday, or Friday with 2- or 3-day interdialytic period and continued for two weeks to ensure a broad range of clinical scenarios.
- Vancomycin infusion was modelled to be given either intradialytically (infuse over the last two hours of HD) or postdialytically (infuse after HD over one to two hours) with the maximum dose of 4g per each administration.

2. MCS and Probability of Target Attainment (PTA)

- Pharmacodynamic (PD) target was AUC_{24h} of 400-700 mg*h/L using MRSA species with MIC of 1 mg/L.
- MCS was performed to calculate AUC_{24h} for the Zelenitsky weight-based intradialytic vancomycin regimen in 5,000 modelled patients in high-flux HD.
- Many intradialytic & postdialytic doses were simulated to determine the loading (LD) & maintenance doses (MD) achieving the PD target in most patients.

3. Development of TDM-guided Dosing Algorithm

- An algorithm using TDM prior to the third dose was developed to individualize the subsequent dosing to attain/maintain AUC_{24h} of 400-700 mg*h/L.

Results

Table 2. Mean AUC_{24h} during a Week of Zelenitsky's Vancomycin Dosing for HD

Body Weight	Vancomycin Dosing	Mean AUC_{24h} (mg*h/L)						
		Day 1 (Mon)	Day 2 (Tue)	Day 3 (Wed)	Day 4 (Thu)	Day 5 (Fri)	Day 6 (Sat)	Day 7 (Sun)
40-70 kg	1,000mg LD, 500mg MD	359.2	329.6	414.9	346.2	392.7	362.2	315.5
70-100 kg	1,250mg LD, 750mg MD	283.5	268.8	428.3	357.4	392.4	361.9	315.4
100-150 kg	1,500mg LD, 1,000mg MD	231.7	219.5	366.9	306.0	344.7	317.8	276.8

*Dosing was modelled to be infused on Monday, Wednesday, & Friday.

Table 3. MCS-Derived Vancomycin HD Dosing Achieving Mean AUC_{24h} 400-700 mg*h/L and TDM-Guided Dosing Algorithm

	Dialyzers	LD (mg/kg)	*MD (mg/kg)	TDM & Dose Adjustment Algorithm
Intradialytic dosing	High-flux	35	15	1. Draw pre-HD level prior to the 2nd MD 2. Adjust the dose using the following equation: New MD (mg/kg) = Previous MD x 20 / Pre−HD Vancomycin concentration
	Low-flux	30	7.5	
Postdialytic dosing	High-flux	25	10	
	Low-flux	25	7.5	

*Any MD falling on Friday is multiplied by 130% to account for 3-day interdialytic period.

Table 4. AUC_{24h} with the Recommended Initial Intradialytic Dosing and Subsequently Individualized Dose in 5,000 Modelled Patients Receiving High-Flux HD

AUC_{24h} (mg*h/L)	D-1 (Mon)	D-2 (Tue)	D-3 (Wed)	D-4 (Thu)	D-5 (Fri)	D-6 (Sat)	D-7 (Sun)	D-8 (Mon)
<400	6.1%	9.1%	2.8%	11.0%	0%	0%	1.0%	0%
400-500	15.2%	18.3%	11.0%	19.3%	1.9%	9.0%	27.4%	7.1%
500-600	22.8%	23.6%	17.8%	23.2%	26.3%	37.8%	38.4%	59.9%
600-700	19.5%	19.2%	20.4%	18.1%	35.1%	30.9%	22.1%	26.5%
>700	36.5%	29.9%	48.0%	28.4%	36.7%	22.2%	11.3%	6.5%
Mean AUC_{24h} (mg*h/L)	659.9	625.4	725.4	614.1	677.4	628.1	569.94	581.1

Initial Recommended LD and MD Adjusted Dose with TDM

*Red box indicates the proportion attaining the PD target of AUC_{24h} of 400-700 mg*h/L

Discussion/Conclusion

- Commonly referenced Zelenitsky's regimen is unlikely to attain desired AUC targets.
- MCS suggests that more aggressive dosing is initially required to achieve AUC_{24h} of 400-700 mg*h/L for the majority of patients receiving maintenance HD.
- HD with high-flux dialyzer resulted in higher vancomycin clearance and required a higher doses to attain the PD target.
- Three-day interdilaytic maintenance dose was 30% higher than two-day interdialytic dose.
- Intradialytic vancomycin dosing yielded a larger interpatient variation in calculated AUC_{24h}, compared with postdialytic dosing.
- TDM and dose adjustment based on Pre-HD serum concentration can guide clinicians to individualize the subsequent dosing that are likely to achieve or maintain the target AUC_{24h} of 400-700 mg*h/L.
- TDM should be conducted every week to determine the dose attaining the PD target.
- The limitation of this study includes using one compartment model due to lack of PK data.
- These results warrant clinical validation.

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