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Central Georgia Infectious Diseases

Vancomycin Dosing by AUC_{24}/MIC in Comparison to Traditional Trough Dosing in Office Infusion Centers (OICs)

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Abstract

Background: New vancomycin (VAN) guidelines have been published with recommendations that dosing in patients (pts) with methicillin-resistant *S. aureus* (MRSA) infections be guided by VAN area under the concentration-time curve from 0 to 24 h to MIC ratio (AUC_{24}). The guidelines emphasize daily AUC_{24} values should be between 400-600 mg*h/L to maximize efficacy and minimize likelihood of acute kidney injury (AKI). Our physicians and clinical pharmacists currently use trough levels to manage outpatient VAN dosing with a general target of 15-20 mg/L. The current pharmacokinetic (PK) model provides an option for dosing using trough or calculated AUC_{24}.

Methods: We identified pts receiving VAN for *S. aureus* infections (default MIC of 1 μg/mL) from 2018-2020. We conducted a PK evaluation of pts with ≥1 trough level and compared it to model predicted AUC_{24}. Data collected included pt characteristics, VAN regimen, trough concentrations, PK evaluation, and AKI, defined as a 50% decrease in CrCl from baseline. A Bayesian PK model was used to calculate predicted dosing based upon trough concentrations (DoseMeRx®, Moorestown, NJ).

Results: 100 pts (mean age: 61±15 yrs, 62% male) from 6 OICs were included, with 82% treated for *S. aureus* infection. Mean initial dose of VAN in the OIC was 2.6±1 g/d in divided doses, most frequently every 12 hrs (68%). Median duration of outpatient therapy was 28 days [IQR, 16-36]. 69% received VAN in the hospital prior to the OIC. 100 pts had 239 trough levels with a corresponding PK analysis. Mean trough levels were 17.1±6.4 mg/L. Mean corresponding AUC_{24} was 498±98 mg*h/L. The relationship between trough and AUC_{24} is shown in Fig 1. 25 evaluations indicated an AUC_{24} < 400, with 8 (32%) resulting in a dose increase. 13 evaluations indicated AUC_{24} > 600, with 6 (46%) resulting in a subsequent dose decrease. 4 pts developed reversible AKI, all with AUC_{24} > 540. Use of AUC_{24} for dosing provided opportunities to adjust dosing in 38/239 evaluations (16%).

Conclusion: This PK evaluation showed a correlation between trough levels and AUC_{24} with opportunities for VAN dose adjustment using AUC_{24}, and to identify pts at risk for developing AKI. Dosing with AUC_{24} is particularly useful in the outpatient setting in which true trough evaluations can be difficult to obtain.

Objectives

Newly-released consensus guidelines for vancomycin (VAN) treatment of *S. aureus* infections recommend switching from trough-based monitoring to AUC-based guidance. AUC_{24} levels of 400-600 mg*h/L are the currently accepted target for efficacy and avoidance of toxicity.[1] This study was designed:

- to evaluate the relationship between VAN trough-based dosing in the outpatient setting and predicted AUC_{24} when calculated using a Bayesian pharmacokinetic (PK) modelling software (DoseMeRx®)[2]
- to determine opportunities and value of AUC_{24}-guided dosing vs. trough dosing in the outpatient setting with potential for reduction in renal insufficiencies

Methods

Study Design and Patient Population:

- Retrospective cohort study
- Pt had ≥4 days of VAN outpatient therapy between 2018 and 2020
- Pt with ≥1 VAN trough level and PK analysis
- *S. aureus* infection confirmed by culture (default MIC=1 μg/mL)

PK analysis:

- VAN trough concentrations were used to perform PK analysis utilizing Bayesian PK modeling software (DoseMeRx®, Moorestown, NJ), which provided predicted AUC_{24}

Data collection:

- Demographics, anthropometrics, infection type, *S. aureus* subtype, site of VAN initiation, baseline renal function parameters, VAN trough concentrations, VAN dose regimen with changes, and changes in renal function
- Comparative analysis: PK analysis was performed based on VAN trough levels and dosing. AUC_{24} for these trough calculations were available using DoseMeRx® and compared to observed trough levels. The desired therapeutic range was defined as AUC_{24} between 400-600 mg*h/L.
- Additional analyses of troughs vs. AUC_{24} were performed for various VAN trough levels, VAN dosing, and for changes in renal function
- Analysis of predicted AUC_{24} was performed for infection types treated and VAN dosing frequencies.

Data Analysis:

- Descriptive statistics

Study Population

- Standard of care in POICs includes PK evaluation prior to initiation of VAN utilizing Bayesian software. VAN trough levels are routinely drawn weekly in the outpatient setting, although pt scheduling and drug self-administration may make it challenging to obtain true trough levels.
- Pts previously hospitalized were initially evaluated using hospital trough levels and inpatient VAN dosing regimens.
- Pts initiated in the POIC had initial PK analysis performed based on population parameters with individualized dosing following the first VAN trough concentration.
- 100 pts who received VAN for confirmed *S. aureus* infection in the outpatient setting were included in the comparative analysis of VAN dosing by AUC_{24} *vs.* traditional trough dosing.

Table 1. Demographics

Parameter	Results (N=100)
Age in years (mean±SD)	61±15
≥65 years	45 (45%)
Gender, male	62 (62%)
Anthropometrics (mean ± SD)	
Ideal body weight (kg)	68.4 ± 11.8
Total body weight (kg)	88.3 ± 21.6
Body mass index (kg/m^2)	28.7 ± 5.9
Body mass index ≥30 kg/m^2	35 (35%)

Data presented as no. of pts (%) unless otherwise indicated.

Table 2. Clinical Characteristics

Clinical Characteristics	Results* (N=100)
Infection type	
Bone and joint (BJI)	54 (54%)
Complicated skin and soft tissue (cSSTI)	19 (19%)
Bacteremia	13 (13%)
Cardiac	6 (6%)
Respiratory	3 (3%)
Other[a]	5 (5%)
Staphylococcus aureus subtype	
Methicillin-resistant (MRSA)	82 (82%)
Methicillin-sensitive (MSSA)	18 (18%)
Site of vancomycin initiation	
Hospital	69 (69%)
OIC	31 (31%)
Baseline renal function parameters	
Serum creatinine (mean ± SD)	0.9 ± 0.4 mg/dL
Creatinine clearance (CrCl), mean ± SD[b]	81.8 ± 33.3 mL/min
CrCl >50 mL/min	86 (86%)
CrCl: 30-50 mL/min	12 (12%)
CrCl <30 mL/min	2 (2%)

*; Data presented as no. of pts (%) unless otherwise indicated.
[a] meningitis (n=1), compl. intraabdominal (n=2), sinusitis (n=1), otitis media (n=1),
[b] CrCl as defined by DoseMeRx[2]

Results

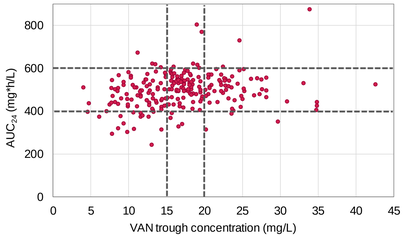
Table 3. Vancomycin Dose Regimen

Variable	Results* (N=100)
VAN dose (g/d), mean ± SD	2.6 ± 1
Duration of therapy in days, median [IQR]	28 [16-36]
Frequency of dosing (n, %)	
Q24	54 (22%)
Q12	147 (62%)
Q8	32 (13%)
Other*	6 (3%)
VAN trough levels per pt, mean ± SD	2.4 ± 1.3

*; including Q36 (n=2), Q48 (n=2), Q18 (n=1), 3 times a week (n=1)

Figure 1. Relationship between Trough and AUC_{24}

- A total of 239 VAN trough concentrations were obtained from 100 pts and evaluated for corresponding AUC_{24}.



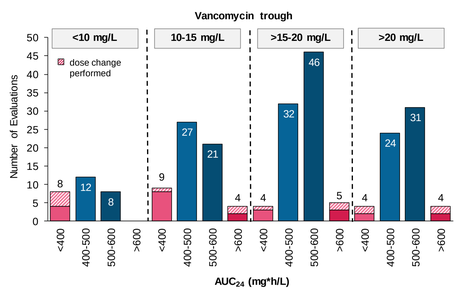
– – current recommended targeted VAN trough and AUC_{24} therapeutic ranges.

Table 4. Distribution and Values of Trough and AUC_{24}

Trough (mg/L)	<15	15-20	>20
No. of evaluations (n/N, %)	89 (38%)	87 (36%)	63 (26%)
Mean ± SD	11.2 ± 2.6	17.3 ± 1.3	25.2 ± 5.5
AUC_{24} (mg*h/L)	**<400**	**400-600**	**>600**
No. of evaluations (n/N, %)	25 (10%)	201 (84%)	13 (5%)
Mean ± SD	353.2 ± 41.5	502.1 ± 49.9	677.9 ± 93.2

- VAN trough distribution was actually highest for troughs <15 mg/L, consistent with dosing in the outpatient setting for more moderate infections.
- Even with varied trough distribution, the large majority of AUC calculations were within 400-600 mg*h/L.
- Overall mean VAN trough was 17.1±6.4 mg/L and mean predicted AUC_{24} was 498.6±98 mg*h/L.

Figure 2. Predicted AUC_{24} by Vancomycin Trough Ranges



- All 239 evaluations were grouped into 4 VAN trough ranges to compare with their corresponding AUC_{24}:
  - troughs >15-20 mg/mL yielded therapeutic AUC_{24} in 90% (78/87)
  - troughs 10-15 mg/L yielded therapeutic AUC_{24} in 79% (48/61)
  - sub-therapeutic troughs (<10 mg/L) yielded therapeutic AUC_{24} in 71% (20/28)
  - supra-therapeutic troughs (>20 mg/mL) yielded therapeutic AUC_{24} in 89% (55/62)
- For AUC levels outside the therapeutic range of 400-600 mg*h/L, we documented measured VAN troughs and determined, if a dose adjustment was performed:
  - 25 evaluations had AUC_{24}<400, of which 8 resulted in dose increases (32%)
  - 13 evaluations had AUC_{24}>600, of which 6 resulted in dose decreases (46%)
  - If AUC_{24} had been used as a dosing guide, an additional 17 evaluations (7%) would have resulted in dose changes

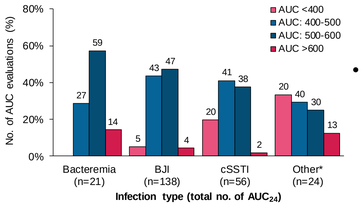
Table 5. Changes in Renal Function

Patient No.	eCrCl (mL/min)*			Predicted AUC_{24} (mg*h/L)	Measured Trough (mg/L)
	Baseline	at Time of Dose Evaluation	Decrease from Baseline		
#1	58.9	26.7	55%	545.0	27.5
#2	97.5	52.6	46%	540.0	16.8
#3	176.2	93.7	47%	558.6	24.8
#4	62.2	31.9	49%	541.1	23.3

*; eCrCl calculated using Cockroft-Gault using the lower of ideal body weight based on metric units or total body weight.[4]

- 4 pts experienced a decrease in CrCl from baseline, 3 with VAN trough concentrations greater than 20 mg/L. VAN dose was decreased in all pts. AUC_{24} dosing per guidelines would not have resulted in changes in these cases.
- The mean predicted AUC_{24} in these pts was 546.2 mg*h/L

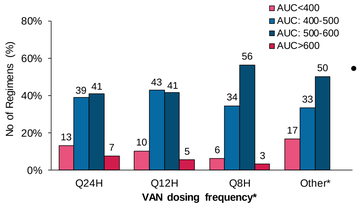
Figure 3. AUC_{24} by Infection Type



- AUC_{24} target levels of 400-600 mg*h/L were observed in pts with bacteremia (86%), BJI (90%), cSSTI (79%), and other infections (70%).

*; including cardiac infection, respiratory infection, intraabdominal infection, and CNS infection.

Figure 4. AUC_{24} by Vancomycin Dose Frequency



- AUC_{24} target levels of 400-600 mg*h/L were achieved with the following dose frequencies: Q24H (80%), Q12H (84%), and Q8H (90%).

*; including Q18 (n=1), Q36 (n=2), Q48H (n=2), and 3 times a week (n=1).

Conclusion

This evaluation demonstrated a 90% correlation between targeted VAN troughs (15-20 mg/L) and model-predicted AUC_{24} (400-600 mg*h/L) using Bayesian PK modeling software.[2]

We found opportunities for dosage adjustments with use of AUC_{24} over VAN trough dosing, but in <10% of evaluations.

The numbers were small, however, all notable serum creatinine increases requiring intervention occurred with AUC_{24} levels <600 mg*h/L.

Overall, PK analysis of VAN dosing by AUC_{24} in the outpatient setting showed similar results to traditional trough dosing. AUC_{24} may be useful when true trough concentrations are difficult to obtain.

References

1. Rybak MJ, Le J, Lodise TP, et al. *Am J Health-Syst Pharm* 2020; 77: 835–64
2. https://doseme-rx.com/
3. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. *Am J Health-Syst Pharm.* 2009; 66(1): 82-98.
4. Buelga DS, del Mar Fernandez de Gatta M, Herrera EV. et al. *Antimicrob Agents Chemother.* 2005;49(12): 4934-4941.