Multicentre Cohort Study Comparing Efficacy and Safety Outcomes with Continuous Infusion Vancomycin and Intermittent Infusion Vancomycin – A Retrospective Study

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ABSTRACT

Background

Patients with good renal function receiving intermittent infusion vancomycin (IIV) may require total daily doses ≥4g to achieve trough concentrations of 15-20mg/L, increasing the risk of vancomycin associated nephrotoxicity (VAN). Continuous infusion vancomycin (CIV) may enable attainment of concentrations between 15-20mg/L with a lower daily vancomycin dose, potentially reducing the risk of VAN.

Objectives

The primary objective was to compare VAN risk (serum creatinine (sCr) increase ≥50% from baseline) and renal damage (sCr increase ≥100% from baseline) in patients receiving IIV versus CIV. The secondary objective was to compare clinical cure between cohorts.

Methods

Retrospective chart reviews for eligible patients admitted to Sunnybrook Health Sciences Centre Bayview or Holland Orthopaedic and Arthritic Campuses between January 1, 2010 and December 31, 2016 were completed. Adult inpatients who received at least 48 hours vancomycin for a documented gram positive infection and had at least one steady state vancomycin concentration were eligible. Baseline patient characteristics, safety and efficacy outcomes for the IIV and CIV cohorts were compared using appropriate statistical tests (Fisher's exact, Student's t-test, or Mann-Whitney), with significance defined as P<0.05.

Results

Of 2134 patients identified, 1104 (52%) met inclusion criteria. Chart review has been completed for 89 patients (113 courses of vancomycin). Patients receiving IIV were more likely to be at risk of VAN (15/62 [24%] versus 4/51[8%]; P=0.02) and experience renal damage (9/62 [15%] versus 1/51 [2%]; P=0.02). There was no difference in clinical cure between IIV (19/27 [70%]) and CIV patients (13/17 [76%]; P=0.74) who attained trough or steady state concentrations of ≥15mg/L, respectively.

Conclusion

Patients in the IIV cohort were more likely to experience increases in serum creatinine resulting in VAN risk and renal damage. The results of the study indicate there is no difference in clinical cure between patients who received IIV versus CIV.

BACKGROUND

- Vancomycin is a glycopeptide antibiotic used to treat resistant gram-positive bacterial infections, including methicillin resistant *Staphylococcus aureus* (MRSA), *Enterococcus faecium*, and coagulase negative Staphylococcus (CNST)
- Vancomycin exhibits time dependent killing, where bactericidal activity is optimized when serum concentration is 3-5 times the minimum inhibitory concentration (MIC)
- AUC_{24}:MIC is the pharmacokinetic/pharmacodynamic parameter that best predicts microbiological and clinical outcomes
- Studies have suggested that AUC_{24}:MIC ≥ 400 may be associated with improved patient outcomes
- Current guidelines recommend targeting a trough of 15-20mg/L as a surrogate for AUC_{24}:MIC ≥ 400
- There is growing interest in dosing certain antibiotics by continuous infusion instead of traditional intermittent infusion
- Dosing by continuous infusion may be beneficial for antibiotics that exhibit time dependent killing, such as vancomycin
- Continuous infusion allows attainment of serum concentrations above the MIC with lower total daily doses, therefore lowering the risk of nephrotoxicity
- To date, studies conclude CIV has comparable safety and efficacy to IIV
- One gap in the literature is the comparison of safety and efficacy of CIV versus IIV where both regimens target a concentration of 15-20mg/L

OBJECTIVES

Primary:

To compare the risk of nephrotoxicity, as defined by the RIFLE criteria, between IIV and CIV

Secondary:

To compare the rate of clinical cure between the IIV and CIV cohorts

METHODS

Study Design

- Retrospective chart review of inpatients at Sunnybrook Health Sciences Centre Bayview (SB) and Holland Orthopaedic and Arthritic Centre (HC) campuses between January 1, 2010 and December 31, 2016

Inclusion Criteria

- Adult (age ≥18 years) patients were included if they:
  - Received a minimum of 48 hours of vancomycin
  - Had documented gram positive infection
  - Had at least one vancomycin steady state level reported
    - ≥ 12 hour dose interval: prior to third dose at earliest
    - ≤ 8 hour dose interval: prior to fourth dose at earliest
    - Continuous infusion: at least 24 hours after dose

Exclusion Criteria

- Switched from vancomycin to another antibiotic based on culture and sensitivity
- Received renal replacement therapy at baseline or immediately prior to initiation of vancomycin
- Had concomitant documented gram negative bacterial, fungal, or viral infection

Outcomes

- Group assignment of patients to IIV or CIV for demographic data was based on the final dosing regimen used for the patient
- Patients who received multiple courses of vancomycin had their demographic data counted once based on data recorded during their first course of vancomycin (e.g. Gender, Age)

Primary outcome:

- RIFLE classification for stratification of severity of acute kidney injury
  - Nephrotoxic Risk: increase in serum creatinine ≥ 50% from baseline
  - Renal Damage: increase in serum creatinine ≥ 100% from baseline
- Each course of vancomycin will be assessed for the risk of nephrotoxicity
- The highest serum creatinine will be assessed according to the dose modality (IIV or CIV) that the patient was receiving at that time

Secondary outcome:

- Evaluate differences in clinical cure in patients receiving IIV and CIV
- Clinical cure was defined as:
  - Resolution of presenting signs and symptoms within 14 days of initiation of vancomycin
  - Maintained resolution of presenting signs and symptoms for 14 days following vancomycin discontinuation
  - No additional antibiotics within 14 days with the same indication as vancomycin
  - Patients were only assessed for clinical cure if they achieved a steady state trough or random level ≥ 15mg/L
  - The time period for assessing clinical cure in patients with prosthetic joint infections was extended to 12 months after completion of final revision
  - Patients with prosthetic joint infection maintained on chronic suppressive antibiotics were still considered a clinical cure

Statistical Analysis

- Data were analyzed using GraphPad InStat (version 3.05, 32-bit for Win95/NT; GraphPad Software Inc, La Jolla, California)
- Fisher's exact test was used to compare nominal data
- Two-sided unpaired t-test was used to compare normally distributed interval data with equal standard deviations
- Two-sided unpaired t-test with Welch correction was used to compare normally distributed interval data with unequal standard deviations
- Two-tailed Mann-Whitney test was used to compare interval data that failed the test for normality
- Statistical significant was defined as P < 0.05.

RESULTS

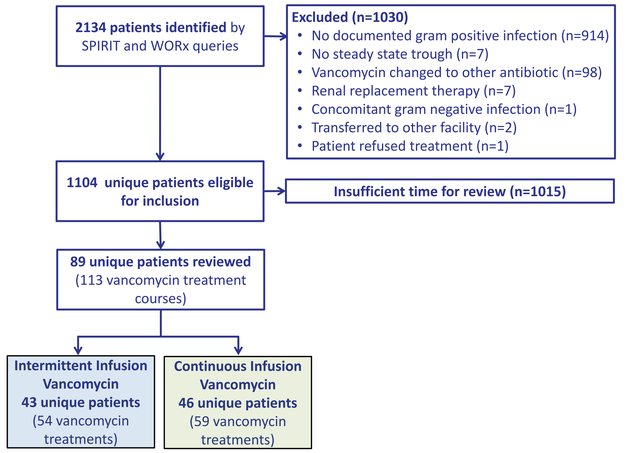

Figure 1. Patient flow through inclusion and exclusion criteria

Table 1: Patient Demographics and Baseline Clinical Factors (N=89)

Patient Characteristic	IIV(N=43) n (% or range)	CIV (N=46) n (% or range)	P-value	Odds Ratio (95% Confidence Interval)
Age (years, mean ± SD)	65 ± 15 (32 - 90)	64 ± 13 (32 - 93)	0.89	- -
Gender (Male)	26 (60%)	22 (48%)	0.29	1.67 (0.72-3.9)
Hospital Site (*HC* versus SB)	23 (53%)	44 (96%)	**<0.001**	0.05 (0.01-0.24)
Hospital Location at Vancomycin Initiation (*Ward* vs. ICU)	33 (77%)	45 (98%)	**0.003**	0.07 (0.009-0.60)
Length of Stay at Vancomycin Initiation (days, median)	4 (0 - 63)	2 (0 - 95)	0.07	- -
Any Comorbidity[a,b]	19 (44%)	9 (20%)	**0.02**	3.30 (1.23-8.55)
Heart Failure	5 (12%)	1 (2%)	0.10	5.95 (0.66-53.22)
Chronic Obstructive Pulmonary Disease	7 (16%)	1 (2%)	**0.03**	8.8 (1.03-74.97)
Diabetes Mellitus	11 (26%)	7 (15%)	0.29	1.93 (0.67-5.56)
Hematological Malignancy	2 (5%)	1 (2%)	0.61	2.2 (0.19-25.21)
Immunosuppression Due to Drug[c]	7 (16%)	2 (4%)	0.08	4.28 (0.84-21.89)
Immunosuppression Due to Drug or Comorbidity[d]	22 (51%)	11 (23%)	**0.009**	3.4 (1.37-8.45)
APACHE II[e] (ICU patients only, ± SD)	20 ± 5 (16 - 30)	18	-	- -
Critically Ill Ward Patients (Pitt[f] ≥ 4)	0 (0%)	0 (0%)	-	- -

IIV: Intermittent Infusion Vancomycin; CIV: Continuous Infusion Vancomycin; HC: Holland Orthopaedic and Arthritic Centre; SB: Sunnybrook Health Sciences Centre Bayview
[a] Patients may have had more than 1 comorbidity, thus totals for specific comorbidities sum to a value greater than the number of patients with any comorbidity
[b] Missing information for 1 patient receiving IIV and 1 patient receiving CIV
[c] Corticosteroids (prednisone >5mg/day, or equivalent), chemotherapy, TNF-α inhibitors, transplant medications
[d] Patients may have had immunosuppression due to drug and comorbidity (n=4), and each patient would only be counted once. Therefore, total in this row may be less than the sum of Any Comorbidity + Immunosuppression Due to Drug values.
[e] Acute Physiology and Chronic Health Evaluation II
[f] Pitt Bacteremia Score

Table 2: Safety Results (N=113)

Outcome	IIV(N=62) n (% or range)	CIV(N=51) n (% or range)	P-value	Odds Ratio (95% Confidence Interval)
Safety Outcomes				
Nephrotoxic Risk[a]	15 (24%)	4 (8%)	**0.02**	3.75 (1.16-12.14)
Renal Damage[a]	9 (15%)	1 (2%)	**0.02**	8.49 (1.04-69.50)
Renal Function Outcomes				
Baseline Serum Creatinine (μmol/L)	80 (24 -234)	72 (35 -142)	0.57	
Highest Serum Creatinine (μmol/L)	88 (28 -454)	78 (42 – 264)	**0.045**	
% Change in Serum Creatinine	25% (-16% - 347%)	10% (-19% – 408%)	**0.0097**	

IIV: Intermittent Infusion Vancomycin; CIV: Continuous Infusion Vancomycin
[a] Safety outcomes assessed based on dose modality (IIV or CIV) patient received at time of highest serum creatinine

Table 3: Efficacy Results (N=89)

Outcome	IIV(N=43) n (% or range)	CIV(N=46) n (% or range)	P-value	Odds Ratio (95% Confidence Interval)
Clinical Outcomes				
Survival	36 (84%)	46 (100%)	**0.02**	0.08 0.004-1.41
Clinical Cure[a]	19 / 27 (70%)	13 / 17 (76%)	0.74	0.73 0.18-2.94

IIV: Intermittent Infusion Vancomycin; CIV: Continuous Infusion Vancomycin
[a] Patients only assessed if they achieved vancomycin steady state trough or random level concentrations ≥ 15mg/L

Table 4. Predicting IIV doses for therapeutic levels

Patient	Initial IIV Total Daily Dose (mg)	Initial Steady State Trough (mg/L)	Final CIV Total Daily Dose (mg)	Final Steady State Level (mg/L)	Predicted IIV dose required to achieve trough 15mg/L (mg)
1	2000	11.49	2000	17.17	2610
2	2000	16.28	1000	19.29	1842
3	2000	9.04	1500	16.25	3318
4	3000	11.64	2750	23.48[a,b]	**3865**
5	2000	7.34	2000	17.07	**4087**
6	2000	18.95	1250	15.09	1583
7	2000	11.64	2000	22.61[a,c]	2577

IIV: Intermittent Infusion Vancomycin; CIV: Continuous Infusion Vancomycin
[a] Neither patient experienced nephrotoxicity
[b] Predicted CIV dose to achieve vancomycin concentration of 15mg/L = 1756mg
[c] Predicted CIV dose to achieve vancomycin concentration of 15mg/L = 1326mg

DISCUSSION

- Unfortunately, the patients included in the preliminary analysis of this study did not have balanced baseline characteristics: more patients in the IIV group were located in the ICU and were more likely to have an underlying comorbidity
- The preliminary results of the study indicate that patients receiving IIV were more likely to have increases in serum creatinine resulting in increased nephrotoxic risk and renal damage compared to patients receiving CIV
- There were no differences in the rate of clinical cure between patients who received IIV and CIV
- The exploration of IIV doses demonstrated that IIV requires greater total daily doses than CIV in order to achieve therapeutic vancomycin levels
- Preliminary results from this study support the use of CIV for patients who are expected to require doses greater than 4g daily to achieve therapeutic levels to minimize exposure to vancomycin and minimize risk of nephrotoxicity

Limitations:

- The current sample size was sufficient to detect a 16% difference in risk of nephrotoxicity as statistically significant (P<0.05)
- However, in order to detect a minimum of a 10% difference in risk of nephrotoxicity and renal damage as statistically significant, we would need approximately 200 patients per group
- Patient baseline characteristics were not balanced in this preliminary analysis: more IIV patients were in the ICU and had underlying comorbid conditions, biasing results against the patients receiving IIV
- Assumptions were made regarding the steady state trough and random vancomycin levels, clinical cure, and clinical failure because of the retrospective nature of the study

Future steps:

- Expand study to additional sites: Michael Garron Hospital and Sunnybrook Health Sciences Centre St. John's Rehabilitation Campus
- Access Infectious Diseases and Holland Centre follow up clinic notes to determine patient's outpatient vancomycin and serum creatinine values
- Complete chart review for 1015 remaining patients at Sunnybrook Bayview Campus
- Match patients according to baseline demographics: gender, age, duration of vancomycin, hospital site, hospital location (ward versus ICU), diagnosis, presence of comorbidities (yes/no)

CONCLUSION

- Preliminary results indicate that patients receiving CIV are less likely to experience an increased risk of nephrotoxicity and renal damage compared to patients receiving IIV
- There were no differences in clinical cure between dosing modalities

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Disclosure:
No author has any conflict of interest related to this study.