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Original Article

Role of Vancomycin Area Under the Curve Trapezoidal Dosing in Prevention of Nephrotoxicity as Compared with Traditional Trough-based Dosing

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ABSTRACT

Background: Vancomycin is a fundamental treatment for resistant gram-positive infections and is implicated in vancomycin-induced-nephrotoxicity (VIN) at high concentrations. Troughs greater than 18 mcg/ml are associated with a 4-fold increase in nephrotoxicity. Additionally, Area Under the Curve/ Minimum Inhibitory Concentration (AUC/MIC) levels over 600 mg*h/L are implicated in VIN. It is proposed that trapezoidal AUC/MIC dosing strategies reduce VIN instances. **Materials and Methods:** Patients greater than 18 years of age who received 72 hr of vancomycin therapy for a non-skin or soft-tissue or urinary indication were included in this retrospective cohort study. The primary endpoint was rate of nephrotoxicity based on the Acute Kidney Injury Network (AKIN) criteria for those patients who suffered an increase in serum creatinine of 0.3 mg/dl or greater after 48 hr of vancomycin therapy. The secondary endpoints were mean 24-hr vancomycin daily doses and instances of trough excursions above 18 mcg/mL between groups. Forty patients met inclusion criteria for the AUC/MIC arm while seventy-nine met inclusion to the trough arm. **Results:** Rates of nephrotoxicity in the trough versus AUC/MIC were 36 patients (30.3%) and 3 patients (7.5%) respectively with a $p<0.001$. AUC/MIC based dosing was associated with decreased rates of nephrotoxicity and decreased rates of trough excursions above 18 mcg/ml. **Conclusion:** The AUC/MIC dosing strategy was associated with lower rates of VIN compared with trough-based dosing.

Keywords: Acute Kidney Injury, Creatinine Clearance, Vancomycin.

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INTRODUCTION

Vancomycin is a fundamental treatment for resistant gram-positive infections.[1] Methicillin Resistant Staph Aureus (MRSA) is the second most common resistant bacterial infection to be acquired in a healthcare facility.[2,3] Infectious processes caused by MRSA can be fatal, particularly in blood stream infections which carry a mortality of up to 40% depending on patient comorbidities.[4,5] Vancomycin has been a mainstay of therapy against many such infections for years, its reputation as a workhorse antibiotic has been well documented, but its ability to cause side effects, in particular Vancomycin induced nephrotoxicity (VIN) should not be underestimated by practitioners.[1] Vancomycin has commonly been dosed using a trough-based method as a more easily obtained surrogate for its AUC/MIC kinetic marker. With the new Infectious Disease Society of America (IDSA) recommendations in 2020, trough based surrogate level dosing has been replaced with a recommendation for use of AUC/MIC marker dosing to reduce nephrotoxicity, while maintaining therapeutic killing effect.[1,3] AUC/MIC based dosing requires two levels, a trough and a peak. This is unique compared with the prior guidelines which previously recommended a trough only approach as a surrogate for AUC/MIC.[1] AUC/MIC trough goals of 400-600 mg*h/L are thought to reduce VIN while maintaining therapeutic effect. As trough-based dosing is still effective, current guidelines recommend its use for skin and soft tissue as well as uncomplicated urinary infections. A lower trough goal of 10-15 mcg/ml is recommended.

Vancomycin induced nephrotoxicity (VIN) is classified as >0.3 mg/ml increase in serum creatinine in a 48-hr period after starting vancomycin based on the Acute Kidney Injury Network (AKIN).[2] Vancomycin is implicated in (VIN) particularly at high concentrations. Troughs greater than 18 mcg/ml are associated with a 4-fold increase in VIN. Additionally, AUC/MIC levels over 600 mg*h/L are implicated in VIN. Evaluations of trough-based dosing have demonstrated that surrogate AUC/MIC levels typically measure over 600 mg*h/L when aiming for the 15-20 mcg/ml target.[6] These AUC/MIC goals should be achieved within 24-48 hr of beginning therapy where possible. Methods to reduce instances of VIN with this important therapy are vital. This study aimed to determine if infections treated with an AUC/MIC based dosing strategy are associated with fewer instances of VIN within our facility.

MATERIALS AND METHODS

IRB approval exemption was granted by the Common Spirit Institutional Review Board (IRB) and was assigned research operating numbers of OHRP IRB00009715 and FWA00019514. Inclusion criteria included any patient over the age of eighteen, who was treated with vancomycin for at least 72 hr. Conversely, those patients who were pregnant, on dialysis, a paraplegic or hemiplegic, and those receiving therapy for skin/soft tissue, genitourinary, or surgical prophylaxis-type indications were excluded. IRB approval was obtained prior to initiation of retrospective data collection. Additionally, the Sanford AUC/MIC trapezoidal calculator was utilized to calculate AUC/MIC dosing strategies. Mann-Whitney tests were utilized to test comparators within separate dosing groups.

This was a one-center retrospective cohort study at Mercy One Medical Center to evaluate the efficacy of the AUC/MIC vancomycin dosing method in reducing VIN rates. Patient data from June 2021 to September

Table 1: Changes in serum creatinine (Scr) in mg/dl in the trough-based arm between two trough measurements of the 72 hr mean level subtracted by the baseline level.

Trough Based Arm Creatinine Increases over 72 hr (mg/dl)				
Average Scr increase of all patients	Scr change without NT agents, troughs >18 mcg/ml	Scr change with nephrotoxic agents	Scr change with troughs > 18 mcg/ml	Scr change with Zosyn as the sole nephrotoxic agent
0.16	-0.02	0.22	0.34	0.26
Total Patients				
n = 79	25% (20)	59% (22 of 37)	50% (41)	26% (21)

Table 2: Changes in serum creatinine in mg/dl in the AUC/MIC based arm between two trough measurements of the 72 hr mean level subtracted by the baseline level.

AUC/MIC Based Arm Creatinine Increases over 72 hr (mg/dl)				
Average Scr increase of all patients	Scr change without NT agents, troughs >18 mcg/ml	Scr change with nephrotoxic agents	Scr change with troughs > 18 mcg/ml	Scr change with Zosyn as the sole nephrotoxic agent
0.03	0.01	0.07	0.01	0.07
Total Patients				
n = 40	8% (3)	21% (4 of 19)	24% (9)	21% (4 of 19)

2021 was collected and analyzed for trough-based dosing. Patient data was also analyzed from November 2021 to February 2022 for AUC/MIC based dosing data. MercyOne informatics specialists accessed and compiled patients in accordance with inclusion criteria. Actual data collection and analysis was performed at MercyOne Medical Center in Waterloo, Iowa in April 2022. Information was de-identified and analyzed with the help of a MercyOne data specialist in April of 2022. Statistical analysis was done using Chi Squared tests for independence with cross tabulation, as well as Mcnemar's tests to determine proportionate serum creatinine changes between groups. Finally, Mann-Whitney U tests were utilized to test for median values of primary and secondary endpoints between groups. The Statistical Package for the Social Sciences (SPSS) was utilized to conduct statistical analysis.

The primary outcome was rates of nephrotoxicity of 0.3 mg/ml increase in serum creatinine in 72 hr measured using two creatinine levels. Secondary outcomes included vancomycin drug level excursions above 18 mcg/ml during vancomycin therapy. An additional secondary endpoint was total daily dose after the initial trough draw. A sub-group analysis was performed for those patients on concomitant nephrotoxic agents with trough excursions greater than 18 mcg/ml.

Baseline Characteristics: 79 patients met inclusion criteria for the trough-based dosing arm, 40 patients met inclusion criteria for the AUC/MIC based dosing arm for 119 patients' total.

Of those, there were 37 (47%) patients on at least one nephrotoxic agent in the trough-based arm. Of the AUC/MIC arm there were 19 (48%) on at least one nephrotoxic agent. Patients were considered to have been on nephrotoxic agents if they received piperacillin-tazobactam, aminoglycosides, or renally cleared dye at any point during their first 72 hr on vancomycin therapy.

RESULTS

Ultimately, 40 AUC/MIC patients were compared with 79 trough-based patients. VIN rates were compared between AUC/MIC and trough-based arms. Between the arms, 3 (8%) of patients in the AUC/MIC arm suffered VIN (Table 2), vs 36 (45.6%) in the trough arm ($p < 0.001$). The AUC/MIC method was associated with being statistically less likely to cause nephrotoxic injury compared with the trough-based method. The secondary outcome was examined as excursions of troughs greater than 18 mcg/ml. For trough excursions > 18 mcg/ml in the first 72 hr of treatment, 9 (18%) of patients in the AUC/MIC arm had an excursion (Table 2) versus 41 (51.9%) in the trough arm ($p=0.004$), (Table 1). The AUC/MIC method was associated with being statistically less likely to generate a trough excursion greater than 18 mcg/ml compared with trough-based dosing. An additional secondary outcome of troughs > 18 mcg/ml in patients on a concomitant nephrotoxic agent (NT) was evaluated. Nineteen patients in the AUC/MIC arm had NT agents, of those, 4 (21%) had VIN (Table 2) while, thirty-seven patients in the trough-based arm had NT agents, of those, 22 (59%) of patients had VIN ($p = 0.085$) (Table 1). Patients were numerically associated to be more likely to receive a nephrotoxic injury while on a NT agent with trough-based dosing versus AUC/MIC based dosing. An additional secondary endpoint was total daily doses calculated between groups for the first full day after troughs were drawn. Of the groups, a total daily dose (TDD) of 1930 mg was identified in the AUC/MIC arm vs 1962 mg in trough arm ($p = 0.11$). There appears no statistically significant difference in TDD after the first trough draw between the arms.

DISCUSSION

This retrospective research adds to the body of data pointing to the benefits of AUC/MIC dosing by demonstrating statistical significance in AUC/MIC based dosing methods as being correlated with the reduction of nephrotoxic injuries.[1,6] In this study, decreased incidences of nephrotoxicity and trough excursions greater than 18 mcg/ml was associated with AUC/MIC dosing. No correlations were drawn regarding the AUC/MIC dosing method's TDD size with traditional trough-based dosing in this study. TDD was seen to be relatively lower than expected in the trough-based arm as TDD was reduced greatly after treatment initiation in response to nephrotoxic injuries. This study was conducted using the Sanford AUC/MIC two level trapezoidal dosing software. AUC/MIC dosing using Bayesian single level monitoring is also commonly used, but two-level monitoring is recommended by the Infectious Disease Society of America (IDSA) at this time[1,6,7] As for limitations of the study, TDD was not observed as an initial TDD but rather after as a TDD after the first trough was drawn. Due to the large number of early nephrotoxic incidents and trough excursions above 18 mcg/ml, it is possible that the total daily dose for the trough-based dosing arm would have been much higher for the initial dosing. Additionally, the trough-based arm "n" value was double that of the AUC/MIC arm. Patient weight and comorbidities were not evaluated as confounders. Patient weight may have contributed greatly to differences in TDD for both treatment arms as vancomycin

dose strength is typically based on actual patient weight. Further, patients with greater dosing weights tend to receive larger doses and demonstrate altered kinetics compared to those with a more typical dosing weight. Distribution curves may be unusually elevated and achieving steady state may take several doses or days in heavier patients. Future studies may benefit from further investigating correlated initiation TDD between the dosing methods. Additionally, a spike in SARs-COV-19 occurred in the study facility during the time period from which data was drawn for trough-based dosing. Though ICU or critical care status was not originally recorded for these patients, it is proposed by the authors that patients from the trough-based arm could generally be much more ill and more likely to sustain an increase in serum creatinine from acute illness or imminent death than those patients in the AUC/MIC arm. Patients with many comorbidities or other illnesses have traditionally demonstrated more difficulty in clearing vancomycin.[1,2] Subjectively, patients in the trough-based arm were simply more critical with a larger number of associated comorbidities, which may help to explain its elevated rates of nephrotoxicity compared with other studies.[1,7] This retrospective study was limited by small sample size which may have obfuscated some statistical relationships while magnifying others, namely the elevated difference in nephrotoxicity rates. Ultimately this data indicates a correlation and statistical significance of AUC/MIC superiority in preventing nephrotoxicity. Additionally, trough excursions greater than 18 mcg/ml were statistically significantly higher in the trough-based dosing arm. This may indicate that trough-based dosing may cause more trough excursions which are associated with increased nephrotoxicity rates.[1,2] A sub-group analysis conducted examined use of nephrotoxic agents concomitant with vancomycin therapy. When using the trough-based method rather than AUC/MIC, use of a concomitant nephrotoxic agents such as piperacillin-tazobactam or aminoglycosides with vancomycin therapy was statistically more likely to be correlated with a nephrotoxic injury. This aligns with prior hypotheses pointing to AUC/MIC superiority and demonstrates its effectiveness at the local host site hospital in reducing nephrotoxicity rates. AUC/MIC based dosing seems to be correlated with reduced rates of nephrotoxicity, reduced rates of trough excursions greater than 18 mcg/ml, and may be more safe when using concomitant nephrotoxic agents than when using trough-based dosing. This study was completed utilizing therapies in accordance with current IDSA guidelines.[7] The 400-600 mg*h/L goals were utilized in accordance with IDSA guidelines and other studies.[1,8,9] Average initial treatment doses were 15-20 mg/kg for both arms based on pharmacist clinical judgement, and per hospital policy and to align with current studies and guidelines.[10] To date, few studies have investigated the relationship between AUC/MIC and reduction in renal toxicity, fewer still have investigated relative treatment failure between the two treatment arms against MRSA or other relevant infections.[11,12] Future studies regarding these topics could shed additional light on advantages of AUC/MIC regarding efficacy as well as safety.[13,14,15]

CONCLUSION

The use of AUC/MIC based dosing therapy did appear associated with reduced rates of nephrotoxicity and rates of trough excursion levels greater than 18 mcg/ml in this patient population at this facility. This adds to the current body of data and research offering inference into the statistical superiority of the AUC/MIC method over traditional trough-based dosing. Ultimately, no significant differences were found regarding TDD of vancomycin. This data helps confirm the utility of recent facility policy changes to pursue AUC/MIC as a treatment monitoring option of choice for using vancomycin to treat MRSA.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AKIN: Acute Kidney Injury Network; **AUC/MIC:** Area under the curve / minimum inhibitory concentration; **CrCl:** creatinine clearance; **NT:** agents nephrotoxic agents; **TDD:** total daily dose; **VIN:** vancomycin induced nephrotoxicity.

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