Utilization of Vancomycin Loading Doses in Patients with Renal Impairment

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Abstract

Purpose: Evaluate the effectiveness of vancomycin 20 – 25 mg/kg loading doses in achieving target therapeutic concentrations after one dose in patients with renal impairment.

Methods: Pharmacists responsible for dosing vancomycin used larger loading doses of 20 – 25 mg/kg per our institution's guidelines. The rate of attaining therapeutic concentrations after the intervention was collected and compared to pre-intervention data. The primary endpoint was rate of achieving target vancomycin concentrations pre- versus post-intervention. Secondary endpoints included time to next dose, timing of level following the dose and, using pooled data, success rate based on doses < 20 mg/kg versus ≥ 20 mg/kg.

Results: One-hundred three patients were included in the pre-intervention (PRE) group and 97 in the post-intervention (POST) group. Average dose was significantly higher in the POST group (16.7 mg/kg ± 3.3 v 21.8 mg/kg ± 4.3, p < 0.0001). Overall, there was a non-significant increase in rate of attaining therapeutic levels following intervention (58.3 % (60/103) v 70.1 %, (68/97), p = 0.08). There was a significant increase in percent therapeutic vancomycin concentrations (34.1 % v 61.9 %, p = 0.006) when targeting 15-20 mcg/mL. When levels were within or below target range, average time to next dose was not different (6.1 hours ± 2.45 v 5.5 hours ± 2.0, p = 0.14). Doses ≥ 20 mg/kg were more likely to achieve therapeutic concentrations if used when targeting 15 – 20 mcg/mL (36.4 % [16/44] v 61.7 % [37/60], p = 0.011). Vancomycin concentrations were more likely to be therapeutic the quicker they were drawn following dose administration for both target concentrations.

Conclusion: Utilization of larger loading doses of vancomycin in patients with renal impairment significantly increased the rate of achieving therapeutic concentrations after the first dose when targeting higher levels. Doses ≥ 20 mg/kg of total body weight were more likely to achieve higher target concentrations.

INTRODUCTION:

Optimal dosing of antibiotics in patients with multidrug-resistant pathogens is essential. Vancomycin remains the gold standard for treatment of many gram positive infections, including methicillin-resistant Staphylococcus aureus (MRSA). Its efficacy has been associated with maintaining trough levels between 10 – 15 mcg/mL or 15 – 20 mcg/mL, depending on the site of infection.[1],[2] Targeting of these trough levels can be complicated in patients with renal impairment because they may exhibit altered pharmacokinetics with respect to volume of distribution and elimination.[1],[2],[3],[4],[5] Given the unpredictability of vancomycin kinetics in this population, our institution's guidelines recommend giving an initial dose, checking a level within 24 hours (generally done with labs the following morning), and re-dosing when the level is within the target range.

A medication use evaluation (MUE) was conducted to assess our institution's ability to reach and maintain target vancomycin concentrations in patients with renal impairment. [6] The MUE results showed that when targeting a trough range of 15 – 20 mcg/mL, levels drawn following the first dose were subtherapeutic approximately 63 % of the time. Achieving trough concentrations within 15 – 20 mcg/mL approximates an area-under-the-curve to minimum inhibitory concentration ratio (AUC/MIC) ≥ 400,

which has been associated with higher clinical cure rates.[2],[7] Therefore, in an attempt to decrease the time to steady-state concentration, higher loading doses (25 -30 mg/kg) have been advocated by the Infectious Diseases Society of America (IDSA) and American Society of Health-System Pharmacists (ASHP) for patients with severe infection.[1],[2] Authors of our institution's guidelines recommend a more conservative loading dose of 20 – 25 mg/kg. However, our MUE found that clinical practice deviated from our institution's guidelines because loading doses were rarely utilized, averaging 16.7 mg/kg total body weight.[6]

In an effort to improve our ability to reach therapeutic target levels in a timely manner, several methods were used to increase the utilization of larger loading doses of 20 – 25 mg/kg in patients with renal impairment as recommended by our institution's guidelines. These methods included educational sessions, grand rounds, newsletters, department emails, and a dosing chart [Table 1] with recommendations for several e easy sentence such as ...nto one easy sentence since I'on, and wouldn't is? "with with forf patients with renal impairment based on total body weight, with a maximum dose of 3000 mg. This present study compared the rate of achieving target vancomycin concentrations prior to and following the educational interventions.

Table 1

Vancomycin Weight-Based Loading Doses

40-44 kg	45-54 kg	55-64 kg	65-74 kg	75-84 kg	85-94 kg	95-104 kg	105-114 kg	≥115 kg
1000 mg	1250 mg	1500 mg	1750 mg	2000 mg	2250 mg	2500 mg	2750 mg	3000 mg

MATERIALS AND METHODS:

Patient Population

This was a single-center, pre- and post-intervention study that was approved by our institution's Human Investigation Committee. Consultations for pharmacy services to dose vancomycin for suspected or confirmed infection in adult patients (i.e., ≥ 18 years) admitted to Beaumont Hospital (Royal Oak, MI) during the two study periods (April 2013 – July 2013 and March 2014 – April 2014) were reviewed for eligible subjects. Patients were eligible for inclusion if calculated creatinine clearance (CrCl) was < 30 mL/min (Cockcroft-Gault equation) or serum creatinine (SCr) was elevated ≥ 0.5 mg/dL from baseline at the time of consultation, or if, based on the pharmacist's discretion, acute changes in renal function would make pharmacokinetics difficult to predict and the patient would benefit from our institution's renal impairment dosing guidelines. Patients were excluded if they were receiving any form of renal replacement therapy (intermittent hemodialysis, peritoneal dialysis or continuous renal replacement therapy), if they had received a dose of vancomycin in the past seven days, or if a level was not drawn following the first dose. Levels were considered therapeutic if concentrations were within or above the target range for the suspected site of infection.

Intervention

Our institution's guideline use of a 20 – 25 mg/kg loading dose in patients with renal impairment based on total body weight, with a maximum one-time dose of 3000 mg, was recommended by educational sessions and grand rounds, as well as distribution of newsletters, department emails, and a dosing chart [Table 1].

Data Collection

Data collection included patient demographics, type/site of infection, target vancomycin concentration, SCr, estimated CrCl (mL/min) based on the Cockcroft-Gault Equation, vancomycin dose (mg and mg/kg) and level (mcg/mL), and time elapsed until next vancomycin dose (hours), if applicable.

Endpoints

The primary endpoint was the rate of achieving the target vancomycin concentration between the pre- and post-intervention. Secondary endpoints included time elapsed to next dose, rate of achieving target concentrations based on doses < 20 mg/kg versus ≥ 20 mg/kg and timing of level following dose, for which the latter were examined using a combined data approach.

Statistical Analysis

A research institute biostatistician completed all analyses. Rate of achieving target vancomycin concentrations when targeting 10 – 15 mcg/mL or 15 – 20 mcg/mL pre-intervention were compared to success rates of their respective targets post-intervention. Descriptive statistics were determined for all data collected. Categorical variables are reported as counts and percent (%) frequencies, and were examined using Pearson's Chi-square tests where appropriate (expected frequency>5); otherwise, Fisher's Exact tests were used. Continuous variables were examined for normality. Normally distributed variables were analyzed

using Student t-tests, and non-normally distributed variables were examined using non-parametric Wilcoxon rank tests. All continuous variables are reported as means +/- the standard deviation (SD) or median +/- interquartile range (25th, 75th percentiles).

RESULTS:

Patient Demographics

There were 103 patients included in the pre-intervention (PRE) group and 97 in the post-intervention (POST) group. Patients had similar baseline characteristics in terms of age, total body weight, and estimated CrCl. There were more males and targets of 10 – 15 mcg/mL in the PRE group compared to the POST group [Table 2].

Table 2

Patient Demographics

	PRE (N = 103)	POST (N = 97)	P-value
Male, n (%)	57 (55.3)	39 (40.2)	0.03
Age, years (mean ± SD)	72.1 ± 15.5	74.0 ± 14.1	NS
TBW, kg (mean ± SD)	85.3 ± 26.5	84.0 ± 31.1	NS
CrCl, mL/min(mean ± SD)	30.1 ± 18.7	28.3 ± 13.6	NS
Target 10 – 15 mcg/mL, n (%)	62 (60.2)	34 (35.1)	0.0004

SD = standard deviation; NS = not significant; TBW = total body weight

Primary Outcome

Overall, there was an improvement in rate of achieving target concentrations following our intervention, but this did not reach statistical significance (58.3 % [60/103] v 70.1 % [68/97], p = 0.08). Targets of 10 – 15 mcg/mL were achieved 74.2 % (46/62) of the time in the PRE group and 85.3 % (29/34) of the time in POST group (p = 0.21). When targeting 15 – 20 mcg/mL, there was a significant increase in percent therapeutic vancomycin concentrations following the intervention (34.1 % [14/41] v 61.9 % [39/63], p = 0.006) [Table 3].

Table 3

Primary Outcome

	PRE (N = 103)	POST (N = 97)	P-value
Dose, mg/kg (mean ± SD)	16.7 ± 3.3	21.8 ± 4.3	<0.0001
Target 10 – 15 mcg/mL, n (%)	46 (74.2)	29 (85.3)	NS
Target 15 – 20 mcg/mL, n (%)	14 (34.2)	39 (61.9)	0.006

SD = standard deviation; NS = not significant

Secondary Outcomes

The average dose used post-intervention was significantly higher than those in the pre-intervention period (16.7 mg/kg ± 3.3 v 21.8 mg/kg ± 4.3, p < 0.0001). Four patients received the maximum dose of 3000 mg, all of whom were in the POST group. When eligible for an additional dose immediately (i.e., level within or below target range), average time to next dose did not differ significantly (6.1 hours ± 2.45 v 5.5 hours ± 2.0, p = 0.14). Seven of the 97 patients (7.2%) in the POST group had vancomycin concentrations > 25 mcg/mL, six of which were drawn < 10.5 hours after the dose and the remaining one was following a loading dose of 31.8 mg/kg.

A compiled analysis of all data found that doses of ≥ 20 mg/kg were more likely to achieve therapeutic concentrations if used when targeting 15 – 20 mcg/mL (36.4 % [16/44] v 61.7 % [37/60], p = 0.011). This difference was not observed when targeting lower concentrations (10 – 15 mcg/mL: 78.3 % [54/69] v 77.8 % [21/27], p = 0.96). The vancomycin concentration was more likely to be therapeutic the sooner it was drawn after the dose was given for both target concentrations [Tables 4 and 5].

Table 4

Secondary Outcomes, Target 10 – 15 mcg/mL

	Therapeutic (N = 75)	Non-Therapeutic (N = 21)	P-value
Dose ≥ 20 mg/kg, n (%)	21 (28)	6 (28.6)	NS
Time of level following dose, n (%)			0.009
≤ 8 hours	13 (92.9)	1 (7.1)	
> 8 – 16 hours	43 (86.0)	7 (14.0)	
> 16 – 24 hours	15 (65.2)	8 (34.8)	
> 24	4 (44.4)	5 (55.6)	

NS = not significant

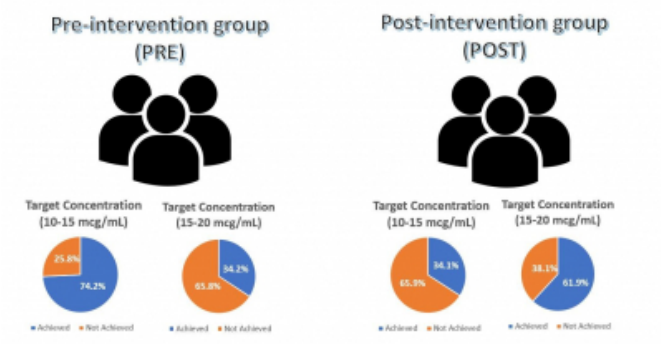
Table 5

Secondary Outcomes, Target 15 – 20 mcg/mL

	Therapeutic (N = 53)	Non-Therapeutic (N = 51)	P-value
Dose ≥ 20 mg/kg, n (%)	37 (69.8)	23 (45.1)	0.011
Time of level following dose, n (%)			0.03
≤ 8 hours	7 (77.8)	2 (22.2)	
> 8 – 16 hours	32 (59.3)	22 (40.7)	
> 16 – 24 hours	10 (32.3)	21 (67.7)	
> 24	4 (40.0)	6 (60.0)	

Figure 1

Comparison of pre-intervention and post-intervention groups.



DISCUSSION:

Methicillin-resistant Staphylococcus aureus infections remain a major cause of morbidity and mortality which may exceed 55 percent in certain illnesses.[8],[9],[10],[11] While several agents have been developed with activity against the resistant organism, vancomycin has remained the gold standard of treatment for more than 50 years.[1],[12] Despite extensive clinical experience, there is limited evidence related to specific dosing and monitoring of vancomycin, particularly in patients with renal impairment. In this population, vancomycin pharmacokinetic parameters are altered with respect to both volume of distribution and clearance. [1],[2],[3],[4],[5] These alterations present a difficult challenge to avoid unwanted toxicities while optimizing therapeutic effect in the setting of increasing minimum inhibitory concentrations (MIC) and variable tissue penetration.[2],[13],[14],[15],[16],[17],[18]

Given the unpredictable kinetics of vancomycin in renal impairment, our institution's guidelines recommend a "dose-by-level" approach where a level is drawn and evaluated within 24 hours following the initial dose. An MUE was conducted to assess the efficacy of this practice and found that targeting higher therapeutic troughs (i.e., 15 – 20 mcg/mL) corresponded with subtherapeutic levels roughly two-thirds of the time, with subsequent doses given an average of six hours later. This is concerning as concentrations that fall below target level are incapable of achieving adequate drug exposure in many types of infection and in isolates with higher MIC values.[2],[19] More specifically, trough levels <15mg/L in patients with MRSA infections requiring 15-20 mcg/mL, per IDSA and ASHP guidelines,[1],[2] may be associated with higher microbiologic and treatment failure.[20] Given the severity of invasive MRSA infections and high frequency of isolates with an MIC >1 at our institution (~75 %), we sought a means to improve rates of achieving target vancomycin concentrations.

There are two principal reasons that explain why subtherapeutic vancomycin concentrations might be observed: the dose was too low or too much time elapsed before drawing the level following drug administration. For logistical and operational reasons, it seemed impractical to have all levels drawn within a shorter timeframe (e.g., < 8 hours). Therefore, we elected to emphasize utilization of loading doses of 20 – 25 mg/kg which were already established in our institution's guidelines. Following this intervention, data collected over two months were analyzed and showed that success rates almost doubled for higher target concentrations. In a pooled analysis of all patients, doses ≥ 20 mg/kg were more likely to achieve therapeutic concentrations. The increase in success rate was not significant for lower target levels as ability to achieve these concentrations were already high pre-intervention. It was observed, however, that longer times to level evaluation were associated with decreased success rates, irrespective of target concentration.

Unfortunately, this study was designed as an MUE and did not examine outcomes or safety data. However, given the relationship between vancomycin trough concentration, MIC, and treatment failure, one could conclude that patients who were maintained with concentrations within the target range had a greater probability of positive clinical outcome.[7],[21],[22] However, this assertion has been challenged.[23]Additionally, there could be concern for increased risk of vancomycin nephrotoxicity associated with higher loading doses. There have been mixed reports of nephrotoxicity associated with vancomycin loading doses ≥ 25 mg/kg, which are recommended per Infectious Diseases Society of America (IDSA) and American Society of Health-System Pharmacists (ASHP) clinical practice guidelines in "seriously ill" patients.[1],[2],[24],[25] However, our guidelines only recommend 20 – 25 mg/kg loading doses with average doses of 21.8 mg/kg post-intervention. It would also be difficult to identify the causal relationship between vancomycin and nephrotoxicity as this patient population had renal impairment and multiple comorbidities prior to drug administration that may have contributed.

Our approach to defining a level as "therapeutic" was conservative in that as long as the level was at or above the lower end of target range (e.g. ≥ 10 mcg/mL for target 10 – 15 mcg/mL) it was considered therapeutic. One must also

remember the average turnaround time for the next dose was between five and six hours. Therefore, a level of 10.1 mcg/mL was considered therapeutic, but by the time the next dose was actually administered it is likely it would have fallen out of the defined therapeutic range. Conversely, levels above the target range were considered therapeutic, but might be concerning for high "troughs." For the same reason, the time it takes the lab to process a blood sample and the pharmacist to evaluate it and dispense a dose, the serum concentration will likely still be within therapeutic range. It was rare for levels to exceed 25 mcg/mL, occurring in only seven patients (7.2 %) in the post-intervention group. Six of these levels were drawn within a short time following the dose (< 10.5 hours) and the remaining one was the result of a loading dose of 31.8 mg/kg.

This study has several limitations including a small sample size. A power analysis was not conducted to detect a difference, but would not have been feasible given the nature of the study and the timeframe allotted for it to be conducted. Patients eligible for the study during the two month follow-up period were evaluated for inclusion until the list was exhausted. Additionally, as stated previously, there were no outcome or safety data collected. The information obtained from this study will nonetheless be useful in contributing to the sparse pharmacokinetic literature describing increased loading doses of vancomycin in patients with renal impairment. Also, the criteria for renal impairment leave some subjectivity to the definition, but this generally reflects real-world practice. Finally, there were many confounding variables that may have contributed to the ability to achieve target concentrations. While dose and timing of level can be modified through operational changes, patient-specific characteristics, including age, infection, severity of renal impairment, obesity, and comorbidities, make it exceedingly difficult to account for and would require a trial on a much larger scale to adequately stratify these patients to detect a difference.

CONCLUSION:

Vancomycin continues to be the gold standard for treatment of invasive MRSA infections. Variability in tissue penetration and increasing MICs make it essential to optimize dosing strategies, particularly in renal impairment when pharmacokinetics are altered. Following recommendations for utilization of loading doses, the rate of achieving therapeutic concentrations after a first dose was significantly increased when targeting higher levels. Larger, prospective studies are necessary confirm the efficacy and safety of this practice.

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