A specially tailored vancomycin continuous infusion regimen for renally impaired critically ill patients

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Abstract

Background: Vancomycin remains the gold standard for treatment of methicillin-resistant *Staphylococcus aureus*. Specially designed continuous infusion of vancomycin leads to better therapy.

Methodology: A total of 40 critically ill patients who suffered from pneumonia susceptible to vancomycin, had serum creatinine >1.4 mg%, and oliguria <0.5 mL/kg/h for 6 h were included in the study with respiratory culture sensitivity to vancomycin ≤2 mg/L. Patients' clinical, microbiological, and biological data were obtained by retrospective analysis of the corresponding medical files before and after vancomycin treatment. Patients with serum creatinine level ≥4 mg% and patients who received renal replacement therapy during the treatment period were excluded. The patients were divided into two groups—group 1 (intermittent dosing) and group 2 (continuous infusion) based on the following formula: rate of vancomycin continuous infusion (g/day) = [0.0205 creatinine clearance (mL/min) + 3.47] × [target vancomycin concentration at steady state (µg/mL)] × (24/1000). Trough vancomycin serum levels were also assessed using high-performance liquid chromatographic technique. Patients' outcomes such as clinical improvement, adverse events, and 15-day mortality were reported.

Results: Group 2 showed significant reduction in blood urea nitrogen, creatinine serum levels, white blood cells, partial carbon dioxide pressure, body temperature, and Sequential Organ Failure Assessment score, while significant increase in partial oxygen pressure and saturated oxygen was also observed. A significantly shorter duration of treatment with a comparable vancomycin serum levels was also reported with group 2.

Conclusion: After treatment, comparison in patients' criteria supports the superiority of using continuous infusion of vancomycin according to this equation in renally impaired patients.

Introduction

Infections in critically ill patients occur frequently and may lead to the development of sepsis or septic shock.[1] Septic shock is associated with 35%–65% of total hospital mortality.[2] The healthcare staff always face the clinical challenge for the best antimicrobial choice in treating critically ill patients due to the emergence and spread of different multiresistant microorganisms.[3] This created a great need to update knowledge of factors involved in the selection of multiresistance and in the patient's clinical response to reach the maximum efficacy of empirically selected antibacterial treatments and to minimize the appearance of multiresistant microorganisms.[3]

In developing countries, *Staphylococcus aureus* is increasingly recognized as an important cause of serious sepsis, and this causes mortality, which far exceeds that in developed countries.[4,5] Methicillin-resistant *S. aureus* (MRSA) represents a great danger for public health worldwide.[6] It is a

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significant cause of health-care-associated and community-associated infection.[7]

After more than 50 years of widespread clinical use, vancomycin still has a major role in the treatment of multidrug-resistant Gram-positive bacterial infections, and it is the drug of choice in the treatment of MRSA infection.[8]

Vancomycin exhibits time-dependent, rather than concentration-dependent, killing capacity.[9] Also, vancomycin should be dosed based on total body weight and creatinine clearance (CLCr).[10] For a long time, vancomycin has been considered a nephrotoxic and ototoxic agent.[11]

Recent vancomycin therapeutic monitoring guidelines recommend accurate adaption of vancomycin dosing regimens to maintain vancomycin trough concentrations between 15 and 20 µg/mL, to achieve optimal target serum vancomycin concentrations and improve patients' clinical outcomes.[12]

Conventional dosing regimens of 1 g every 12 h have little evidence supporting their efficacy in treating specific populations, particularly in the critically ill patients.[13] The continuous infusion of high-dose vancomycin combination therapy is an effective, trustable, and reasonably safe treatment of chronic MRSA.[14]

The aim of this study was to evaluate the currently used vancomycin intermittent dosing regimen versus especially tailored continuous infusion based on patients' kidney function in critically ill patients.

Patients and methods

This was a prospective randomized parallel study, with equal numbers of patients in each group and balanced characteristics. The study was conducted in Critical Care Medicine Department, Cairo University Hospitals, Egypt. Informed consent was obtained from all subjects or their surrogate after explaining the nature, purpose, and potential risks of the study. The study was approved by the research and ethics committee of Faculty of Pharmacy, Cairo University, which followed the tenets of the Declaration of Helsinki.[15]

In this prospective study, respiratory samples of adult patients, susceptible to vancomycin treatment on culture basis, were taken and cultured for microorganism identification (*S. aureus*), before and after treatment and the minimum inhibitory concentration (MIC) was calculated. The bacteria showing MIC ≤2 mg/L for vancomycin were considered sensitive. Antibiotic sensitivity, identification of isolated strains, and MIC were determined by Microscan apparatus (Dade Behring Inc.).

Patients with serum creatinine >1.4 mg% associated with oliguria <0.5 mL/kg/h for 6 h were included in the study. Patients who underwent dialysis, experienced systolic blood pressure <90 mmHg, and patients who suffered from critical cases potentially resulting in renal dysfunction (e.g. septic shock, cardiac arrest) while on vancomycin therapy in the hospital were excluded.

All recruited patients were subjected to complete physical examination including body weight, heart rate (HR), respiratory rate (RR), and body temperature. All the subjects were also screened biochemically and microbiologically. These screens included electrolytes, complete blood count (CBC), kidney function tests, liver function tests, arterial blood gases (ABG), and microbiological evaluation.

Clinical assessments using Simplified Acute Physiology (SAP), Acute Physiology and Chronic Health Evaluation (APACHE II), and Sequential Organ Failure Assessment (SOFA) scores were performed.

Recruited patients were randomly divided into two groups to receive one of the following dosing regimens:

Group 1: patients received intermittent bolus doses as ordered by physicians based on actual body weight and CLCr as 20 mg/kg every 12 h for CLCr of 80–100 mL/min, 18 mg/kg every 12 h for CLCr of 70 mL/min, 25 mg/kg every 24 h for CLCr of 50–60 mL/min, 22 mg/kg every 36 h for CLCr of 40 mL/min, and 18 mg/kg every 48 h for CLCr of 30 mL/min.[16]

Group 2: patients received continuous infusion according to the following equation: rate of vancomycin continuous infusion (g/day) = [0.0205 CLCr (mL/min) +3.47] × [target vancomycin concentration at steady state (µg/mL)] × (24/1000).[17]

The total daily dose was administered in polyvinyl chloride bags of 500 mL normal sodium chloride solution 0.9% over 24 h.

A quantity of 3 mL venous blood samples were collected at the steady state in both groups: group 1 samples were collected 30 min before the fourth dose, while group 2 samples were collected 48 h after starting vancomycin therapy. All samples were stored at −80°C until analyzed. Vancomycin plasma concentrations were quantified by high-performance liquid chromatographic (HPLC) assay.[18] The lower limit of quantification for plasma samples was 0.2 µg/mL, the response from calibration standards was linear from 1 to 80 µg, and the coefficient of correlation for all measured sequences was at least 0.9984.

Total vancomycin doses, vancomycin serum levels, and duration of treatment were recorded.

All recruited patients were subjected to daily follow-up where all the previously mentioned evaluations were repeated in all patients at the end of vancomycin therapy. Vancomycin adverse events and 15-day mortality were also monitored and recorded.

Statistical analysis

Student's *t*-test was used for different comparable groups, paired sample *t*-test was used for comparing data within the same group, χ^2 test was used for categorical variables, and Fisher's exact test was used when observations in one

Table 1. Comparison between group 1 and group 2 before vancomycin treatment with respect to kidney function tests, WBCs, ABGs, temperature, and sepsis score.

Parameter (mean ± SD)	Group 1, before treatment	Group 2, before treatment	*p* value
BUN (mg %)	56.2 ± 26.19	46.8 ± 20.27	0.212
Creatinine (mg %)	1.90 ± 0.43	2.01 ± 0.63	0.531
WBCs (C/mm)	13.81 ± 4.81	16.82 ± 13.23	0.347
PCO_2 (mmHg)	42.65 ± 13.94	42.55 ± 11.7	0.981
PO_2 (mmHg)	80.21 ± 35.2	69.3 ± 46.79	0.41
Saturated O_2 (%)	85.52 ± 12.61	76.94 ± 17.8	0.089
Temperature (°C)	37.86 ± 0.85	38.335 ± 1.16	0.144
APACHE II score	12.85 ± 4.21	14.2 ± 4.6	0.339

SD: standard deviation; *p*: level of significance at $p < 0.05$; BUN: blood urea nitrogen; WBCs: white blood cells; PCO_2: partial pressure of carbon dioxide; PO_2: partial pressure of oxygen; APACHE: Acute Physiology and Chronic Health Evaluation.

Table 2. Comparison between group 1 and group 2 after vancomycin treatment with respect to kidney function tests, WBCs, ABGs, temperature, and sepsis score.

Parameter (mean ± SD)	Group 1, after treatment	Group 2, after treatment	*p* value
BUN (mg %)	51.9 ± 27.94	36 ± 18.71	0.041*
Creatinine (mg %)	1.81 ± 0.58	1.3 ± 0.6	0.009*
WBCs (C/mm)	15.01 ± 4.96	9.99 ± 3.78	0.001*
PCO_2 (mmHg)	44.22 ± 13.20	36.07 ± 8.34	0.025*
PO_2 (mmHg)	82.16 ± 36.83	94.45 ± 30.1	0.252
Saturated O_2 (%)	84.36 ± 16.82	94.01 ± 11.03	0.038*
Temperature (°C)	38.21 ± 0.96	37.15 ± 0.42	0.0001*
APACHE II score	10.5 ± 3.85	9.9 ± 5.54	0.611

SD: standard deviation; *p*: level of significance at $p < 0.05$; BUN: blood urea nitrogen; WBCs: white blood cells; PCO_2: partial pressure of carbon dioxide; PO_2: partial pressure of oxygen; APACHE: Acute Physiology and Chronic Health Evaluation.
*Significantly different at $p < 0.05$.

category were less than 5. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as frequency and percentage. All analyses were performed using SPSS software for Windows, version 16 (SPSS Inc., Chicago, IL). Correlations were performed using Spearman's rho. Significance was accepted at the level of *p* <0.05.

Results

A total of 40 patients from those who were admitted to the Critical Care Medicine Department, Cairo University Hospitals, during the period from November 2009 to September 2012 were enrolled in the study. Patients' population showed matched demographics of age, gender, weight, and height plus allergies. All the recruited patients were renally impaired. All patients' criteria were comparable between the two groups before initiation of vancomycin treatment as shown in Table 1.

After the administration of vancomycin, it was found that the average serum creatinine levels, blood urea nitrogen (BUN) levels, white blood cells (WBCs), and ABGs were

significantly different, clinically favoring group 2 dosing regimen over group 1, clearly demonstrated in Table 2.

There was a significant reduction (*p* = 0.0001) in number of feverish patients in group 2 (2 out of 20 patients (10%) of group 2 vs 14 out of 20 patients (70%) of group 1).

When it comes to microbiological comparison, it was found that 11 out of 20 patients (55%) in group 1 who showed positive respiratory cultures before vancomycin administration remained the same after treatment. On the contrary, group 2 started with 12 out of 20 patients (60%) showing positive culture before vancomycin; this percent significantly declined (*p* = 0.003) to 2 out of 20 (10%) after treatment.

It was also found that there was a significant (*p* =0.003) decline in APACHE II score after vancomycin treatment in conventional intermittent group, while there was significant improvement in BUN, creatinine levels, WBCs, partial pressure of carbon dioxide (PCO_2), partial pressure of oxygen (PO_2), saturated O_2, temperature, SAP score, and APACHE II score after vancomycin administration in the continuous infusion group (*p* = 0.004, 0.0001, 0.0001, 0.037, 0.015, 0.02, 0.0001, 0.0001, and 0.001, respectively).

Vancomycin steady-state concentrations were comparable ($p = 0.874$) in both groups 1 and 2 (18.72 ± 8.14 vs 18.13 ± 14.15 µg/mL, respectively). When the patients were categorized according to vancomycin serum levels into subtherapeutics, therapeutic, or supratherapeutics, comparison favored the continuous infusion regimen: 6 patients (30%) had subtherapeutic vancomycin serum levels (<15 µg/mL), 8 (40%) had optimum therapeutic levels (15–20 µg/mL), and 6 (30%) had supratherapeutic levels (>20 µg/mL) in the continuous infusion group, while in the intermittent conventional dosing group, it was found that 11 (55%) had subtherapeutic levels, 2 (10%) were within the optimum range, and 7 (35%) were above the safety margin.

Comparing total vancomycin doses administered during the treatment period, it was found that there was no significant difference ($p = 0.085$) between groups 2 and 1 (9.93 ± 2.21 vs 8.35 ± 3.33 g, respectively). It was observed that duration of therapy was significantly shorter ($p = 0.0001$) in group 2 in comparison to the period elapsed in treatment of group 1 patients (5.05 ± 0.99 vs 9.3 ± 2.99 days).

Adverse events screening demonstrated that the two groups were comparable where two patients (10%) showed allergic reactions, and a single patient (5%) suffered from ototoxicity out of the 20 patients in group 1, which caused termination of therapy, while no adverse events were recorded among those in group 2.

There was no difference between the groups with regard to other antibiotics received or nephrotoxins; 3 patients out of 20 in each group were on additional meropenem antibiotic, and 2 patients out of 20 in each group were on furosemide.

Discussion

Vancomycin is a key antibiotic in the treatment of severe Gram-positive infections. The emergence of MRSA strains with reduced susceptibility to vancomycin has prompted internists to administer high-dose treatment to achieve trough levels of 15–20 µg/mL for adequate antibiotic concentrations at the infection site.[19]

This study focused on evaluating a specially tailored vancomycin continuous infusion regimen based on kidney function and CLCr in critically ill adult patients, diagnosed with Gram-positive infections susceptible to vancomycin. The study used a previously published and validated vancomycin dosing equation. This equation was designed based on the fact that vancomycin is excreted primarily via the kidney as a function of glomerular filtration rate (GFR).[17] This was useful toward adapting an initial vancomycin dosage regimen, without waiting for the result of vancomycin plasma concentration tests available few days later. This approach was beneficial toward faster treatment schedule achievement without vancomycin initial loading doses.[20] Physicians in Critical Care Medicine Department completely refused to give loading doses to renally impaired patients.

This special continuous infusion is proven to be superior in comparison to the intermittent dosing for fewer adverse drug reactions necessitating discontinuation of treatment, 10% suffered from allergic reactions, and 5% suffered from ototoxicity in the intermittent doses group, while no patient was found in the continuous infusion group.

Several studies including those of Vandecasteele and De Vriese,[21] Diamondi and Rafferty,[22] and Pea et al.[23] compare vancomycin continuous infusion to intermittent dosing regimen. In contrast to the current study, the continuous infusion was always applied after an initial loading dose of 15 mg/kg over 2 h, irrespective of the patients' renal function, and this led to an incremental risk of nephrotoxicity associated with higher vancomycin doses in 12%–42.7% of patients, making this a high-risk approach for critically ill patients receiving concomitant nephrotoxic agents and patients with already compromised renal function.[21]

In this study, there was a significant decline in creatinine serum levels after vancomycin treatment, where 75% of the patients in the continuous infusion group returned to be in the normal creatinine level ranges in comparison to 35% in the intermittent doses group. No significant difference in 15-day mortality was recorded. The study results supported what was reported in meta-analysis stating that lower nephrotoxicity was associated with continuous infusion with no statistical significant difference in mortality.[24] There was also a significantly shorter duration of treatment in the continuous infusion group ($p = 0.0001$). Same results were reported by Ingram et al.[25] and Vandecasteele et al.,[26] who supported continuous infusion as it was associated with less and slower onset of nephrotoxicity along with a shorter treatment duration leading to a higher probability that patients could complete treatment courses without nephrotoxicity.

The results were also in agreement with Byl et al.,[27] who favored continuous infusion to reach the target concentrations more quickly and attain more sustained vancomycin concentrations in body fluids, contributing to better prognoses for deep-seated infections and reducing or even preventing the risk of the emergence of vancomycin resistance.

More patients in the continuous infusion regimen were in the optimum therapeutic range compared to those who received intermittent doses. Akers et al.[28] supported the use of continuous infusion for more frequent therapeutic vancomycin levels and less frequent subtherapeutic levels compared to intermittent dosing with a significant increase in mean vancomycin levels.

The study results disagree with the prospective multicenter randomized study performed by Wysocki et al.,[29] which was unable to demonstrate clinical or microbiological improvement favoring continuous infusion as there were no significant differences in clinical outcomes and treatment failure cases while there was a moderate increase in creatinine levels in both groups. This might have been due to the longer duration of therapy (10 days or more); the duration of treatment in this study was about 5 days, as studies state that

the longer the duration of vancomycin treatment, the more possibility of nephrotoxicity.[26]

Conclusion

Adaptation of vancomycin continuous infusion using specially tailored doses without loading doses in the treatment of renally impaired critically ill patients provided clinical superiority to intermittent dosing and no documented nephrotoxicity.

Study limitations

The main study limitation is the small sample size. This could be attributed to the restricted use of vancomycin in renally impaired critically ill patients for the fact that vancomycin is a highly nephrotoxic antibiotic, and the authors had great difficulties convincing the physicians to prescribe it for their patients. The second reason for the small sample size was the nature of the study, which was self-funded.

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