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ORIGINAL ARTICLE

Effect of Vancomycin Administration Method on Achieving and Maintaining Its Serum Concentrations In Intensive Care Patients

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Summary
Introduction. Vancomycin may be administered by bolus injections (BI) and continuous infusion (CI). Data on BI and CI clinical effectiveness and correlation with mortality, survival and renal injury is variable.
Aim of the study. The aim of the study was to compare the use of vancomycin continuous infusion and bolus administration in intensive care.
Materials and methods. Retrospective analysis of 46 ICU patients (23 patients received vancomycin CI and 23 – BI) was undertaken to compare efficacy and effect on mortality and morbidity of these two administration methods.
Results. The study revealed association of CI administration with more effective (15 – 25 mg/L) serum vancomycin trough concentration maintenance (31.2% vs 25.6% of treatment time, p=0.011) as well as with reduced incidence of subtherapeutic vancomycin levels (34.3% vs 37.2% of treatment time, p=0.015). We also observed better survival times using CI mode.
Conclusions. CI appears to be beneficial in terms of better maintenance of target VSTC and better patient survival. However, its use compared to bolus administration has no statistically significant impact on overall mortality and incidence of nephrotoxicity.
Key words: Vancomycin, continuous infusion vs intermittent, subtherapeutic concentrations, mortality, intensive care.

INTRODUCTION

Vancomycin is a glycopeptide antibiotic used for treatment of gram-positive (particularly MRSA) infections. It's characteristic features are narrow therapeutic index and time-dependent rather than concentration-dependent bactericidal effect. (2, 15, 16) Therefore maintaining certain serum trough concentrations is more important for clinical efficacy than reaching certain peak concentrations. (16) In order to improve clinical efficacy and reduce incidence of microorganism resistance in case of severe *S.aureus* infections maintenance of serum trough concentrations of 15 – 20 mg/L is recommended. (15, 16) Data suggesting a direct causal relationship between toxicity and specific vancomycin serum concentrations is limited; its evaluation is complicated by the presence of confounding nephrotoxic agents, variable definitions of toxicity, and inability to examine the time sequence of events surrounding changes in renal function secondary to vancomycin exposure. (15, 16)

At P. Stradins Clinical University Hospital general Intensive Care Unit both vancomycin administration by bolus injections (using conventional doses of 1 – 2 g once or twice daily, depending on vancomycin serum concentrations) and, recently, continuous infusion (over 24 hours using the adapted protocol of Sheffield Teaching Hospitals NHS Trust, United Kingdom, available for public review (7)) is used. The latter involves adjusted weight-specific loading dose administration immediately followed by continuous infusion, which rate is determined considering patient's renal function (urine output, creatinine clearance, serum urea and creatinine, use of renal replacement therapy). Subsequent CI rate adjustments are made daily according to the protocol depending on vancomycin serum trough concentrations (determined every morning and aiming 15 – 25 mg/L).

AIM OF THE STUDY

The aim of the study was to compare the use of vancomycin continuous infusion and bolus administration in intensive care.

MATERIALS AND METHODS

Following approval by the University of Latvia Experimental and Clinical Medicine Institute Ethics Committee, a retrospective study of patients receiving vancomycin for treatment of gram-positive infections was carried out to compare BI and CI administration methods. The study involved case note analysis of randomly selected patients who received vancomycin on our ICU between January and April 2013.

Clinical and demographic data on 46 patients (23 received vancomycin by CI, 23 – by BI) were gathered, including demographics (age, sex), diagnosis, surgeries performed, ICU length of stay, length of artificial ventilation, as well as length of vancomycin therapy, 24 hour doses used, frequency of administration (for BI) and administration rate (for CI), dynamics of daily determined vancomycin serum trough concentrations (VSTC), renal function dynamics (urine output, creatinine clearance, serum urea and creatinine), presence of renal replacement therapy, and clinical outcome (transfer to general ward or death).

CI and BI administration methods were compared in terms of the following:

1) **speed of achievement** of therapeutically effective VSTC (time in days since commencement of vancomycin therapy till trough concentration of >15 mg/L achieved for the first time);
2) **effectiveness for maintenance** of target VSTC: *absolute* (amount of therapy days when VSTC was within the target range) and *relative* time (percentage of days when VSTC was within the target range out of the full length of therapy [in days]);
3) frequency of **subtherapeutic** and **supratherapeutic** VSTC episodes for CI and BI;
4) Differences in patient overall ICU **mortality, survival time** and development of **nephrotoxicity**.

Data were analyzed and statistically processed using SPSS Statistics 20 software.

RESULTS

Age structure of the patients in CI and BI groups (Figure 1) is comparable within the 41 – 80 y.o. range; however, BI group had more patients 18 – 40 y.o. and no patients > 80 y.o.

Length of vancomycin therapy varied between 3 and 21 days: mean 9.74 ± 4.67 days in CI group and 6.17 ± 3.84 days in BI group. Mean ICU stay was 27.65 days in CI group and 19.91 days in BI group.

Overall ICU **mortality** was 30.43% (14 patients): 9 patients (39.13%) in CI group and 5 patients (21.74%) in BI group. Analysis of patient mortality with Fisher test showed no statistically significant association with the use of CI (OR 1.8; p = 0.337). A possible cause of 1.8 fold higher mortality in CI group could be heterogeneity of the study population in terms of diagnosis, age, co-morbidities and baseline physiological state; it is also possible that clinicians were choosing CI for more severely ill patients with initially known worse prognosis.

Analysis of CI and BI groups using Kaplan-Meier **survival curves** showed statistically significant better survival in CI group (Figure 2), e.g. 5-day survival rate was 50% in CI group vs 15% in BI group (p = 0.005 with Mantel-Cox test).

Speed of achievement of therapeutically effective VSTC was faster in CI group, however analysis of the data showed that these results are not statistically significant: CI group 3^{d} [2 – 4] vs BI group 4th [2 – 4] treatment days (p = 0.391 with Mann-Whitney U test).

Maintenance of target VSTC (15 – 25 mg/L) was better using CI (3.7 ± 3.4 days or 47.6 ± 31.2% of treatment time) than BI (1.4 ± 1.6 days or 25.6 ± 26.8% of treatment time). Analysis with Mann-Whitney U test proved statistical significance of these results (p = 0.011).

Frequency of **subtherapeutic** VSTC episodes was higher in BI group – mean 3.1 ± 1.95 days (66.4 ± 34.3% of treatment time) versus 2.1 ± 2.21 days (38.7 ± 37.2% of treatment time) in CI group. Data analysis with Mann-Whitney U test showed statistically significant lower incidence of subtherapeutic VSTC in CI group (p = 0.015; 25 [0 – 71] vs 75 [38 – 100]).

Frequency of **supratherapeutic** VSTC episodes was almost 2 times higher in CI group - mean 1.3 ± 1.68 days (17.3 ± 24.89% of treatment time) versus 0.4 ± 7.22 days (8.1 ± 17.38% of treatment time) in BI group. However, analysis with Mann-Whitney U test showed absence of statistical significance of these data (p = 0.092; (10 [0 – 29] vs 0 [0 – 15]), which means that it cannot be extrapolated to a larger population.

Renal function dynamics were assessed using daily serum creatinine values and the following definition of vancomycin induced nephrotoxicity: serum creatinine increase by ≥44,2 mcmol/L (***or*** ≥50% over baseline) in consecutively obtained daily serum creatinine values ***or*** a drop in calculated CLcr of 50% from baseline on two consecutive days in the absence of an alternative explanation. (4, 6, 8, 9, 10, 17) Patients with initially high baseline serum creatinine levels (>113 mcmol/L) were excluded from further analysis. Due to retrospective nature of our study only serum creatinine levels and not creatinine clearance criterion was used. Figure 3 reflects the incidence of serum creatinine level dynamics corresponding to the above definition of nephrotoxicity in both groups.

Incidence of nephrotoxicity in CI group was 7.1% (1 of 14 patients), but in BI group – 25% (4 of 16 patients). However, analysis with Fisher test shows absence of statistical significance of these data (p = 0.336).

DISCUSSION

Our study results show absence of statistically significant difference in patient mortality between vancomycin CI and BI groups. This is similar to the data from the majority of other studies investigating this correlation. (1, 3, 15, 16, 18, 19) However, one matched cohort study reported lower mortality rates for critically ill patients with ventilator-associated pneumonia receiving vancomycin in CI (25% vs 55%). Multiple regression analysis of the data confirmed that CI was associated with improved survival. (12) The latter corresponds to our results which also show improved survival in CI group.

Faster achievement of effective VSTC which was seen in our study is similar to the data from other scientists (5, 11, 13, 14, 18), however our results on this do not appear to be statistically significant.

As regards CI superiority in terms of lower VSTC variability and its better maintenance within the target range our results match the data of other published studies. (11, 13, 14, 18, 19)

Our study didn't reveal correlation between CI use and lower incidence of nephrotoxicity. We find this difficult to investigate due to wide ICU patient heterogeneity and specific features, such as variable co-morbidities, hemodynamic instability, 24-hour urine output changes, body fluid compartment volume shifts, and therapeutic use of other potentially nephrotoxic agents, which makes it impossible to attribute serum creatinine changes solely to the effect of vancomycin.

CONCLUSIONS

We found the use of vancomycin CI protocol associated with more straightforward and uniform action plan for clinicians, as it provides a simple tool for dose/rate adjustment judging by the daily VSTC measurements and other parameters.

Continuous infusion appears to be beneficial in terms of better maintenance of target VSTC and better patient survival. However, its use compared to bolus administration has no statistically significant impact on overall mortality and incidence of nephrotoxicity.

Conflict of interest: None

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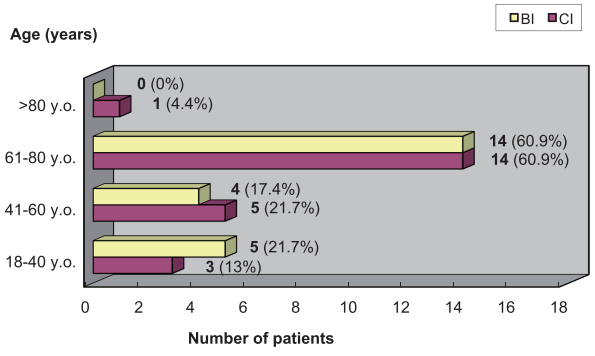

Fig. 1. Patient`s age structure

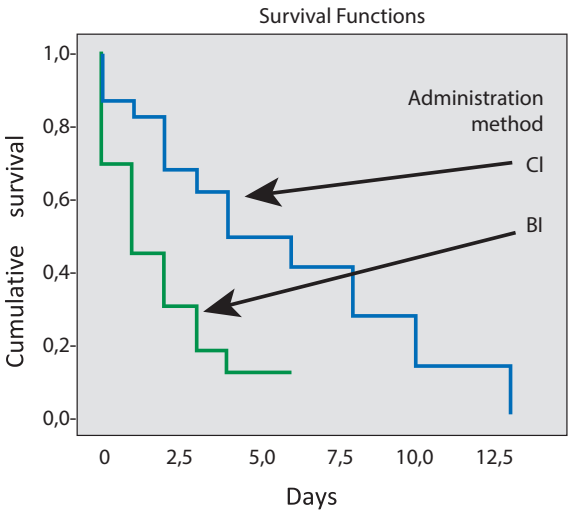

Fig. 2. Patient`s survival in CI and BI groups

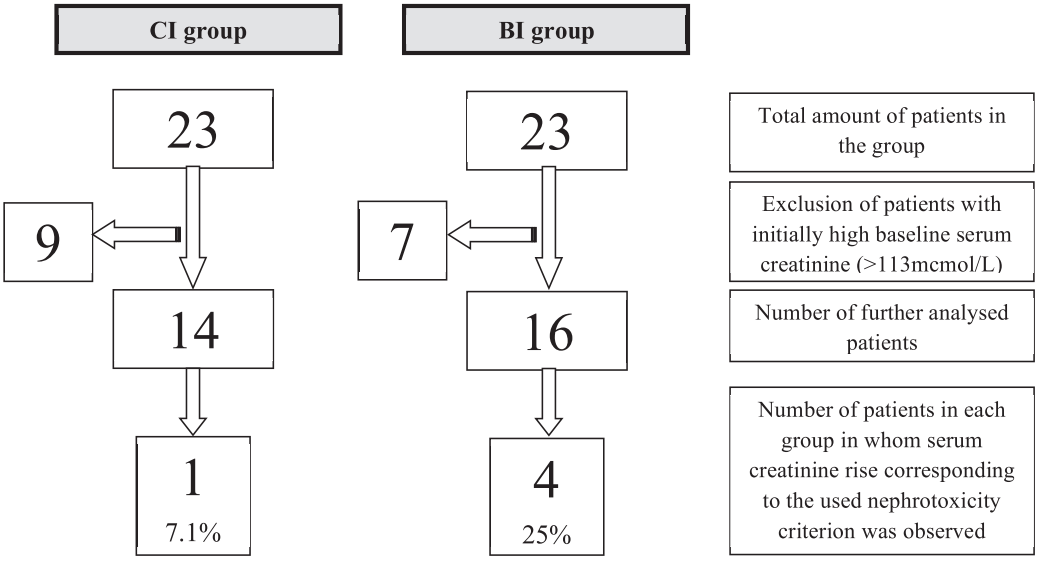

Fig. 3. Evaluation of serum creatinine level dynamics