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Impact of area under the concentration–time curve to minimum inhibitory concentration ratio on vancomycin treatment outcomes in methicillin-resistant *Staphylococcus aureus* bacteraemia

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ABSTRACT

There have been few clinical studies on the association between the vancomycin 24-h area under the concentration–time curve (AUC_{24}) to minimum inhibitory concentration (MIC) ratio and vancomycin treatment outcomes in methicillin-resistant *Staphylococcus aureus* (MRSA) infections. To examine this association and to establish a suitable cut-off value for AUC_{24}/MIC, a multicentre prospective observational study was conducted in patients with MRSA bacteraemia. Data were collected on all patients aged ≥18 years with MRSA bacteraemia treated with vancomycin for ≥72 h without dialysis. The MIC was determined by broth microdilution (BMD) and Etest. Treatment failure was defined as (i) 30-day mortality, (ii) persistent bacteraemia (≥7 days) and (iii) recurrence (≤30 days after completion of therapy). AUC_{24} was estimated by a Bayesian approach based on individual vancomycin concentrations. The AUC_{24}/MIC cut-off value for differentiating treatment success and failure was calculated by Classification and Regression Tree (CART) analysis. In total, 117 patients were enrolled, among which vancomycin treatment failure occurred in 38 (32.5%). In univariate analysis, high vancomycin MIC and low trough levels were unrelated to treatment outcomes. In the CART analysis, low vancomycin AUC_{24}/MIC [<392.7 (BMD) and <397.2 (Etest)] was associated with treatment failure. In multivariate analysis, low AUC_{24}/MIC was a risk factor for treatment failure [adjusted odds ratio (aOR) = 3.50, 95% confidence interval (CI) 1.39–8.82 by BMD; aOR = 5.61, 95% CI 2.07–15.24 by Etest]. AUC_{24}/MIC is associated with vancomycin treatment outcomes in MRSA bacteraemia, and seeking individualised AUC_{24}/MIC ratios above target (>400) may improve treatment outcomes.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is an important disease with high mortality rates and substantial cost to the healthcare system [1,2]. The 30-day all-cause mortality rate of MRSA bacteraemia exceeds 30% and has not changed for two decades [3]. Although vancomycin remains the treatment of choice, there are concerns about its suboptimal efficacy and the optimal dosing strategy [4,5]. Clinical studies have shown an association between treatment outcome and the ratio of the vancomycin 24-h area under the concentration–time curve (AUC_{24}) to minimum inhibitory concentration (MIC) [6–10]. Based on those studies, the Infectious Diseases Society of America (IDSA) and the American Society of Health-System Pharmacists (ASHP) guidelines

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recommend that vancomycin trough levels should reach 15–20 mg/L for optimal antibiotic exposure (AUC_{24}/MIC > 400) in serious MRSA infections such as bacteraemia [11]. In most previous studies, workers did not follow these new target trough levels. This was because of their retrospective nature and the long study periods involved (usually over 5 years) [5,8,9,12,13]. Vancomycin AUC_{24} was usually estimated by a simple formula based on daily vancomycin dose and creatinine clearance in previous studies [8,9,12,13].

In the present study, the association between vancomycin AUC_{24}/MIC and treatment outcomes was examined in a multicentre prospective cohort study with a predefined sample size providing adequate statistical power. The optimal cut-off value of AUC_{24}/MIC in these patients was established by performing a Bayesian estimation based on individual AUC_{24} and measuring the MIC by both broth microdilution (BMD) and Etest in a clinical setting, according to the recent vancomycin dosing guidelines.

2. Patients and methods

2.1. Study population

This prospective cohort study was conducted at Seoul National University Bundang Hospital (a 900-bed tertiary hospital in Seongnam) and Seoul National University Hospital (a 1300-bed tertiary hospital in Seoul). All adult patients (aged ≥18 years) with first MRSA bacteraemia during the study period were screened. Patients who fulfilled the following criteria were excluded: (i) polymicrobial bacteraemia; (ii) immediate transfer to another hospital; (iii) absence of data on treatment outcome; (iv) died within 72 h after index culture; (v) received renal replacement therapy; (vi) received vancomycin for <72 h; (vii) did not receive vancomycin within 5 days of index culture; (viii) vancomycin serum concentration was not checked within the first 5 days of treatment; and (ix) the index MRSA isolate was unavailable.

2.2. Data collection

At least once a week, all adult patients with MRSA bacteraemia were identified in the database of the clinical microbiology laboratory. Demographic characteristics, underlying diseases, primary infection site, vital signs and laboratory findings were collected in uniform case record form using electronic medical records. These included Charlson's weighted index of comorbidities (WIC) [14], presence of risk factors for healthcare-associated infection [15], Pitt bacteraemia score [16] and SOFA (Sequential Organ Failure Assessment) score [17]. High-risk sources of bacteraemia were defined when infections were endovascular, lower respiratory tract or intra-abdominal infections, based on our previous cohort data and references [1,18].

As this was an observational study, vancomycin dosage, interval and frequency of monitoring of vancomycin concentration were not changed. Our institutional dosing guidelines recommend 15–20 mg/kg based on actual body weight every 12 h in adult patients with normal renal function. The guidelines recommend monitoring the vancomycin concentration prior to the fourth or fifth dose in all patients, and if the dosage is changed they recommend therapeutic drug monitoring (TDM) until steady-state is reached. After consensus meetings of infectious diseases specialists, clinical microbiologists, clinical pharmacologists and pharmacists in October 2010, the recommended target trough levels were increased to 15–20 mg/L in MRSA bacteraemia as in the 2009 IDSA/ASHP guidelines [11]. Although individual regimens were ultimately decided by the attending physicians, compliance with these recommendations was nearly total.

2.3. Microbiological and pharmacokinetic/pharmacodynamic (PK/PD) parameters

Only the first positive blood culture isolate from each patient was stored at −70 °C for vancomycin MIC determination. MIC was determined by Etest (AB BIODISK, Solna, Sweden) according to the manufacturer's instructions, and by BMD according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) [19]. Individual pharmacokinetic parameters were calculated using Abbottbase® Pharmacokinetic System (PKS) v.1.10 (Abbott Laboratories, Chicago, IL) [4]. Vancomycin serum levels were fitted to a two-compartment volume clearance model using the maximum a posteriori probability Bayesian approach. The model equations and the Bayesian priors used for the two-compartment analysis in this study are listed in the appendices (Eq. (A), Appendix C). The Cockcroft–Gault equation was used to calculate estimated creatinine clearance (Eq. (B)). This equation estimates the initial steady-state vancomycin clearance (CL_{VM}) and predicts trough levels based on age, sex, actual body weight, creatinine clearance and serum albumin concentration. Vancomycin AUC_{24} was the total vancomycin dose in milligrams for 24 h over the vancomycin clearance. The total vancomycin dose corresponded to dosing for 24 h under initial steady-state conditions.

2.4. Definition of vancomycin treatment failure

Vancomycin treatment failure was defined as (i) 30-day all-cause mortality, (ii) persistent bacteraemia (bacteraemia present despite 7 days of vancomycin therapy) and (iii) recurrence of MRSA bacteraemia within 30 days after completion of antimicrobial therapy.

2.5. Statistical analyses

The required sample size was based on the association between MIC and treatment outcomes in MRSA bacteraemia [6,20]. A treatment failure rate of 45% in the lower AUC_{24}/MIC group and 20% in the higher AUC_{24}/MIC group was estimated, and a 1:2 ratio for the two groups was set. Using a one-sided type I error rate of 0.05, a sample size of 37 for the lower AUC_{24}/MIC group and 74 for the higher AUC_{24}/MIC group (total 111 cases) provided >80% power to detect an increased treatment failure in the lower AUC_{24}/MIC group.

Differences in proportions were compared by Fisher's exact test or χ^2 test, and means were compared by Student's *t*-test or Mann–Whitney *U*-test. Classification and Regression Tree (CART) analysis was used to determine the AUC_{24}/MIC cut-off value for vancomycin treatment failure. All clinically relevant risk factors with *P*-values of <0.20 in the univariate analysis were included in the initial model, and backward stepwise logistic regression analysis was performed to define significant risk factors for vancomycin treatment failure. To avoid data overlap in the multivariate analysis, the Pitt bacteraemia score was included instead of shock. Charlson's WIC and all underlying diseases were analysed in a separate logistic regression model. Multivariate models were reviewed for appropriateness using the Hosmer–Lemeshow goodness-of-fit test. IBM SPSS Statistics for Windows v.20.0 (IBM Corp., Armonk, NY) was used for univariate analysis and logistic regression, and R for Windows (2.13.0/R package-rpart; http://www.r-project.org) for regression tree analysis.

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