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ORIGINAL RESEARCH

Pharmacokinetic/pharmacodynamic analysis of teicoplanin in patients with MRSA infections

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Background: Teicoplanin is a glycopeptide antibiotic that has been used to treat serious, invasive infections caused by Gram-positive bacteria. The area under the drug concentration–time curve (AUC)/minimum inhibitory concentration (MIC) was identified as a pharmacokinetic–pharmacodynamic (PK–PD) parameter of glycopeptide antibiotics that correlated with bacteriological responses and clinical outcomes. Although optimized dosing regimens based on PK–PD are needed, a PK–PD analysis of teicoplanin against methicillin-resistant *Staphylococcus aureus* (MRSA) infections has not yet been performed. Thus, this study examined patients with MRSA infections, who were administered with teicoplanin in order to determine the target AUC/MIC ratio.

Methods: This study retrospectively assessed data obtained as part of our routine therapeutic drug monitoring (TDM) of teicoplanin therapy in 46 patients with MRSA infections at Kagoshima University Hospital. Serum concentrations of teicoplanin were determined using a fluorescence polarization immunoassay system and used for a Bayesian PK estimation to estimate AUC for 24 hours (AUC_{24}). The MIC value for teicoplanin was determined using a standardized agar dilution method. The effects of teicoplanin were evaluated in terms of bacteriological responses by a quantitative assessment.

Results: The estimated AUC_{24}/MIC ratios with and without bacteriological responses were 926.6±425.2 μg·h/mL (n=34) and 642.2±193.9 μg·h/mL, respectively (n=12; $P<0.05$). On the basis of a logistic regression analysis, AUC_{24}/MIC ratios of 500 μg·h/mL, 700 μg·h/mL, and 900 μg·h/mL gave probabilities of treatment success of 0.50, 0.72, and 0.87, respectively. Furthermore, using the Kaplan–Meier curve analysis, an AUC_{24}/MIC ratio of ≥900 led to a significantly stronger bacteriological response than an AUC_{24}/MIC ratio of <900.

Conclusion: These results suggest that an AUC_{24}/MIC ratio of ≥900 μg·h/mL is required to ensure a sufficient bacteriological response.

Keywords: teicoplanin, PK/PD, AUC/MIC, MRSA

Introduction

There has been an increasing interest in pharmacokinetic (PK)/pharmacodynamic (PD) analyses because they are able to optimize dosing regimens, thereby improving outcomes.[1] PK/PD analyses, based on the principle reported by Craig[2] and other researchers to optimize dose regimens for clinical applications, are now increasing in the USA and Europe. Teicoplanin is a glycopeptide antibiotic that has been used to treat serious, invasive infections caused by Gram-positive bacteria.[3] The area under the drug concentration–time curve (AUC)/minimum inhibitory concentration (MIC) has been identified as a PK/PD parameter of glycopeptide antibiotics that correlated

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with bacteriological responses and clinical outcomes.[4,5] The guidelines for therapeutic drug monitoring of vancomycin suggest that an AUC/MIC ratio of ≥400 is the PK/PD parameter associated with clinical and bacteriological responses to vancomycin therapy.[6,7] Although optimized dosing regimens based on PK/PD are needed, the PK/PD analysis of teicoplanin against methicillin-resistant *Staphylococcus aureus* (MRSA) infections has not yet been performed. Therefore, the target AUC/MIC ratio of teicoplanin remains unclear. We herein examined patients with MRSA infections who were administered with teicoplanin in order to determine the target AUC/MIC ratio of teicoplanin.

Methods

Patients

The number of beds at Kagoshima University Hospital is 715. This study retrospectively assessed data obtained as part of our routine TDM of teicoplanin therapy in 46 patients with MRSA infections at Kagoshima University Hospital. This study was approved by the Ethics Review Board of Kagoshima University Hospital (#273).

Patients were excluded if they fulfilled any of the following criteria: children, lack of TDM data, teicoplanin MIC data for MRSA and culture test data, and combination with other anti-MRSA agents.

Teicoplanin was administered intravenously at an initial dose of 200 mg (n=4), 400 mg (n=30), 500 mg (n=2), 600 mg (n=8), and 800 mg (n=2) every 12 hours for three doses. Then, teicoplanin was continued at a maintenance dose of 200 mg (n=14), 300 mg (n=3), 400 mg (n=22), 500 mg (n=1), 600 mg (n=5), and 800 mg (n=1) every 24 hours.

Measurement of teicoplanin trough concentrations

Serum samples were separated from venous blood by centrifugation at 3,000 rpm for 10 minutes, and serum concentrations of teicoplanin were determined by using a fluorescence polarization immunoassay system (TDxFLx analyzer; Abbott Laboratories, Abbott Park, IL, USA).

Creatinine clearance

Creatinine clearance (CL_{cr}) was estimated using the actual body weight value in the Cockcroft–Gault formula.[8]

Estimation of AUC for 24 hours

The serum teicoplanin concentration in each patient was used to estimate individual total clearance (CL_{total}) by using a Bayesian estimation based on the population PK parameters of teicoplanin in the Japanese patients.[9] The mean population PK parameters were as follows: teicoplanin clearance (L/h) =0.00498 × CL_{cr} (mL/min) + 0.00426 × body weight (kg); the distribution volume of the central compartment (L) =10.4; the transfer rate constant from the central compartment to the peripheral compartment (h^{-1}) =0.38; the transfer rate constant from the peripheral compartment to the central compartment (h^{-1}) =0.0485. The AUC value for 24 hours under steady-state conditions was estimated as AUC for 24 hours (AUC_{24}; μg·h/mL) = daily dose (mg)/CL_{total} (L/h).[4]

Teicoplanin susceptibility testing

The MIC for teicoplanin was determined using the standardized agar dilution method according to the Clinical and Laboratory Standards Institute guidelines.[10] A suspension of bacteria equivalent to the 0.5 McFarland turbidity standards was inoculated onto Mueller-Hinton agar plates. An *E*-test for teicoplanin was plated onto the agar. The MIC value was read following 16–20 hours of incubation at 37°C.

Bacteriological efficacy

The effects of teicoplanin in terms of bacteriological responses were evaluated with a quantitative and/or semi-quantitative assessment. The detected MRSA strains were sorted into five levels according to bacterial counts. "Eradication" was defined when bacterial count was zero, "decrease" when bacterial count was decreased by 1–4 levels, and "persistent" when bacterial count remained unchanged or increased. The teicoplanin treatment was then classified as "success" (eradication and a decrease in MRSA) or "failure" (persistent MRSA).

Statistical analysis

A logistic regression analysis was performed to determine whether the teicoplanin AUC_{24}/MIC ratio was a significant predictor of bacteriological responses (1, success; 0, failure). The time from initiation of the teicoplanin treatment to the development of microbiological efficacy was estimated using a Kaplan–Meier curve analysis. All statistical analyses were performed using SPSS software (Version 15.0J; SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics are shown in Table 1. A total of 46 patients, 36 men and ten women, with a mean age of 73.1±9.4 years and body weight of 53.5±10.8 kg, were available for retrospective analysis. The indications for teicoplanin treatment were as follows: wound infection (n=17), pneumonia (n=14), bacteremia (n=6), and others (n=9). The MICs and their percentages of strains were 0.38 μg/mL

Table 1 Characteristics of 46 patients included in the present study

Characteristics	Number or mean ± SD (range)
Sex	
Male	36
Female	10
Age (years)	73.1±9.4 (53–86)
Body weight (kg)	53.5±10.8 (36.0–77.5)
Clinical situation	
Wound infection	17
Pneumonia	14
Bacteremia	6
Others	9

Abbreviation: SD, standard deviation.

(2.2%), 0.5 μg/mL (6.5%), 0.75 μg/mL (43.5%), 1.0 μg/mL (34.8%), and 1.5 μg/mL (13.0%).

The AUC_{24}/MIC ratios with and without bacteriological responses were 926.6±425.2 μg·h/mL (n=34) and 642.2±193.9 μg·h/mL (n=12) ($P<0.05$), respectively. Figure 1 shows the relationship between AUC_{24}/MIC ratios on day 3 and bacteriological responses (failure, 0; success, 1). AUC_{24}/MIC ratios of 500, 700, and 900 μg·h/mL gave probabilities of treatment success of 0.50, 0.72, and 0.87, respectively.

The bacteriological treatment successes were evaluated in 15 patients with AUC_{24}/MIC ratios of ≥900 and 31 patients with AUC_{24}/MIC ratios of <900 using the Kaplan–Meier curve analysis (Figure 2). Patients with AUC_{24}/MIC ratios of ≥900 had significantly stronger bacteriological responses than those with AUC_{24}/MIC ratios of <900 ($P<0.05$).

Discussion

For vancomycin, trough concentrations are used as a surrogate of AUC values. The trough concentrations of 10–20 μg/mL

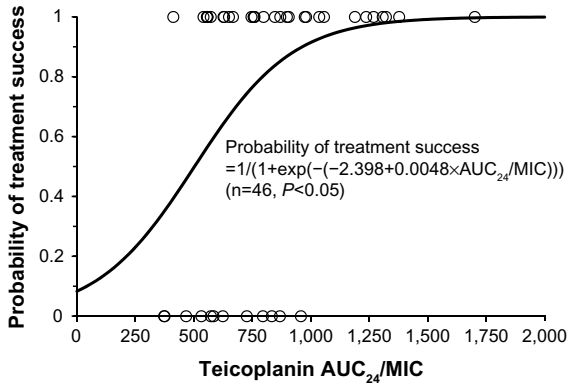

Figure 1 Teicoplanin AUC_{24}/MIC ratio and logistic regression model for bacteriological responses (failure, 0; success, 1).
Abbreviations: AUC_{24}, area under the concentration–time curve for 24 hours; MIC, minimum inhibitory concentration.

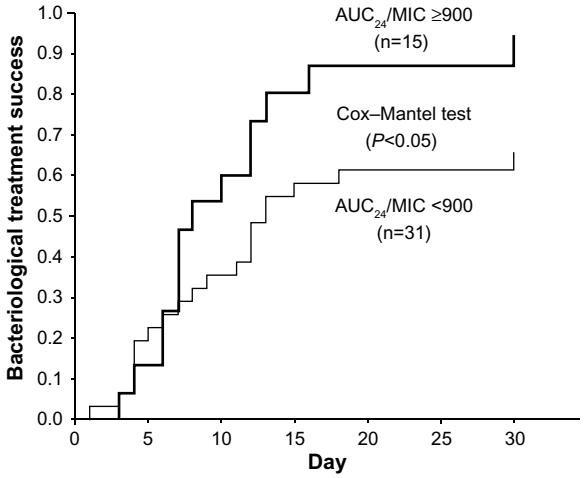

Figure 2 Kaplan–Meier plot showing the time from the initiation of teicoplanin therapy to efficacy rates between the AUC_{24}/MIC ratios of ≥900 (n=15) and <900 (n=31).
Abbreviations: AUC_{24}, area under the concentration–time curve for 24 hours; MIC, minimum inhibitory concentration.

are needed to achieve an AUC value of ≥400.[6] If an AUC/MIC ratio of ≥400 is not achieved, even though an appropriate trough level is achieved, vancomycin treatment would not exhibit a good response. Similar to teicoplanin, previous studies have shown that teicoplanin trough concentrations of >13 μg/mL are effective for treating most infections.[11] However, the teicoplanin treatment should be optimized using AUC/MIC ratios on the basis of PK/PD. Thus, this study examined patients with MRSA infections who were administered with teicoplanin in order to determine the target AUC/MIC ratio of teicoplanin. This PK/PD analysis determined the AUC_{24}/MIC target value of teicoplanin required to cure patients with MRSA infections. The AUC_{24}/MIC ratios of 500, 700, and 900 μg·h/mL showed probabilities of treatment success of 0.50, 0.72, and 0.87, respectively.

Craig previously reported that AUC/MIC ratios may be an important PK/PD parameter that correlates with the efficacy of vancomycin and teicoplanin.[5] Hagihara et al reported that the AUC_{24} value on the third day was significantly higher in the treatment success group (897.6±71.7 μg·h/mL) than that of the treatment failure group (652.9±83.4 μg·h/mL).[12] These findings indicated that an AUC_{24} value of at least 800 μg·h/mL is required to ensure bacteriological responses (MIC of ≤1.0 μg/mL for all isolates).[12] Kanazawa et al also showed that an increase in the probability of treatment success was dependent on AUC_{24} values and that the target that gave a probability of ~0.9 was 750 μg·h/mL (MIC of <2.0 μg/mL for all isolates).[13] They could not estimate AUC_{24}/MIC, because exact MICs were not measured. On the other hand, Ogawa et al indicated that a $\log[C_{max,\ unbound}/MIC]$ of 0.30 on day 3 of

teicoplanin therapy was the threshold for achieving treatment success[14]; however, they did not evaluate AUC_{24}/MIC ratios. The MICs of teicoplanin for a total of 46 MRSA strains were determined in the present study by the *E*-test method. AUC_{24}/MIC ratios were significantly higher in the treatment success group (926.6±425.2 μg·h/mL) than in the treatment failure group (642.2±193.9). An AUC_{24}/MIC ratio of 900 μg·h/mL showed a probability of treatment success of 0.87 (Figure 1). Furthermore, using the Kaplan–Meier curve analysis, an AUC_{24}/MIC ratio of ≥900 exhibited a significantly stronger bacteriological response than that of an AUC_{24}/MIC ratio of <900 (Figure 2). These results suggested that an AUC_{24}/MIC ratio of ≥900 μg·h/mL may be required to ensure bacteriological responses. Therefore, not only trough concentrations but also AUC/MIC ratios should be monitored for teicoplanin TDM.

This study focused on bacteriological responses because clinical outcomes, such as relief from symptoms, reduced white blood cell count, and decrease in body temperature, are dependent on many factors.[12,13,15] However, clinical outcomes are also important for the interpretation and clinical applicability of the current results. Additionally, in this retrospective study, each patient was different in teicoplanin dose, duration of therapy, severity of illness, and type of infections. Therefore, well-designed prospective studies for various types of infection in a larger number of patients are needed to validate the current findings.

Conclusion

This PK/PD analysis revealed the target AUC_{24}/MIC ratios of teicoplanin in patients with MRSA infections on the basis of PK/PD analyses. These results indicated that an AUC_{24}/MIC ratio of ≥900 μg·h/mL is required to ensure bacteriological responses. However, further studies are needed to confirm these results and clarify their therapeutic implications.

Disclosure

The authors report no conflicts of interest in this work.

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