Development of Initial Loading Procedure for Teicoplanin in Critically Ill Patients with Severe Infections

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Meticillin-resistant Staphylococcus aureus (MRSA) is now endemic in many hospitals. Infection with MRSA is more frequent in the intensive care unit (ICU) than in general wards. Therefore, appropriate treatments for MRSA infections will lead to good outcomes in the ICU. Teicoplanin is an anti-MRSA agent. Recently, it was recommended at a new target trough concentration of 15–30 µg/mL. However, the initial loading procedure for teicoplanin to allow it to reach the target concentration promptly remains uncertain. Therefore, this study aimed to determine the appropriate initial loading procedure for teicoplanin in critically ill patients with severe infections. We performed a retrospective study in patients given teicoplanin in the ICU in order to determine the initial loading procedure to promptly reach the target trough concentration. We then evaluated the trough concentration on the third day after commencement of teicoplanin therapy. The mean loading dose and trough concentration were 11.5±1.0 mg/kg and 18.9±5.9 µg/mL, respectively. A correlation (r=0.45, p=0.046) was shown between teicoplanin loading dose and trough concentration. The correlation equation was trough concentration=2.563·loading dose−10.672. In the cases of 11.0 and 15.0 mg/kg for the loading dose, respectively, trough concentrations were 17.5 and 27.8 µg/mL. We suggested that an initial loading dose of 11–15 mg/kg every 12 h for 3 doses should be administered to promptly achieve the target trough concentration of 15–30 µg/mL on the third day after commencement of teicoplanin therapy in the ICU.

Key words teicoplanin; loading dose; trough concentration; meticillin-resistant Staphylococcus aureus

In current dosing strategies, a teicoplanin trough concentration of 20–30 µg/mL for deep-seated Gram-positive infections was targeted.7,8) Thus, we have recommended 15–30 µg/mL as the target trough concentration in the ICU. Recently, Ueda et al.9) also suggested 15–30 µg/mL as the new target. However, the initial loading procedure for teicoplanin to enable it to promptly reach the optimal concentration remains uncertain in critically ill patients with severe infections. Pea et al. recommended that an initial loading dose of 6 mg/kg every 12 h for 3 doses is warranted for critically ill patients10); however, this initial loading procedure could not promptly achieve a trough concentration of >15.0 µg/mL.3,8)

This study aimed to determine the appropriate initial loading procedure for teicoplanin in critically ill patients with severe infections. Therefore, we performed a retrospective study in patients given teicoplanin in the ICU in order to determine the initial loading procedure to promptly reach the target trough concentration; we then evaluated the trough concentration on the third day after commencement of teicoplanin therapy.

MATERIALS AND METHODS

Patients This study was approved by the Ethics Review Board of Kagoshima University Hospital. In the ICU, 20 adult patients with suspected and documented MRSA infections received teicoplanin from July 2005 to September 2010 at Kagoshima University Hospital. Teicoplanin was administered

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intravenously at a dose of 10.0–13.6 mg/kg every 12 h for 3 doses.

**Measurement of Teicoplanin Plasma Concentrations**

Blood samples were taken 18–24 h after the third administration. After centrifugation at 3000 rpm for 10 min, serum concentrations of teicoplanin were determined using a fluorescence polarization immunoassay system (TDxFLx analyzer, Abbott Laboratories, Abbott Park, IL, U.S.A.).

**Assessment of Nephrotoxicity and Hepatotoxicity**

Kidney functions were accessed by serum creatinine, before initiation and after completion of teicoplanin therapy. Nephrotoxicity was defined if values after completion of teicoplanin therapy increased to more than 0.5 mg/dL. Liver functions were accessed by total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) values, respectively, before initiation and after completion of teicoplanin therapy. Hepatotoxicity was defined if values after completion of teicoplanin therapy increased more than 3.0 times.

**Statistical Analysis**

Pearson’s correlation coefficient analysis and simple regression were used to assess the correlation between teicoplanin trough concentration and loading dose.

**RESULTS**

Patient characteristics are shown in Table 1. Thirteen men and 7 women, with a mean age of 69.5 ± 9.5 years (mean ± S.D.), body weight 54.7 ± 8.2 kg, serum albumin 2.8 ± 0.4 g/dL, and serum creatinine 1.2 ± 0.7 mg/dL, were evaluated in this study.

Figure 1 shows the relationship between teicoplanin loading dose and trough concentration on the third day. The mean loading dose and trough concentration were 11.5 ± 1.0 mg/kg and 18.9 ± 5.9 µg/mL, respectively. A correlation (r = 0.45, p = 0.046) was shown between teicoplanin loading dose and trough concentration (range: 9.1–28.7 µg/mL); it was not a high but a statistically significant correlation. The correlation equation was trough concentration = 2.563 × loading dose − 10.672. In the cases of 11.0, 12.0 and 15.0 mg/kg for loading dose, respectively, trough concentrations were 17.5, 20.1 and 27.8 µg/mL.

Eleven patients were documented to have MRSA infections. Patients with MRSA bacteremia and pneumonia were 8 and 3, respectively. Although 3 patients with MRSA bacteremia died, 8 patients were ameliorated by teicoplanin therapy. The cure rate was 72.7%. Nephrotoxicity and hepatotoxicity were each observed in one patient. Serum creatinine in one patient with a trough concentration of 25.6 µg/mL increased from 0.9 to 1.4 mg/dL. Total bilirubin, AST, and ALT in the other patient with a trough concentration of 12.9 µg/mL increased from 0.4 to 6.9 mg/dL, 23 to 85 IU/L, and 17 to 71 IU/L, respectively.

**DISCUSSION**

Teicoplanin should be administered with a loading dose to achieve a steady state early because of its prolonged serum half-life. This study retrospectively analyzed the pharmacokinetics of teicoplanin in critically ill patients with severe MRSA infections in the ICU. The mean loading dose and trough concentration were 11.5 ± 1.0 mg/kg and 18.9 ± 5.9 µg/mL, respectively (Fig. 1). Wilson6) recommended that patients with burns, septic arthritis, and MRSA endocarditis should be given a loading dose of 12 mg/kg every 12 h for 3 doses. We revealed that a loading dose of 12 mg/kg every 12 h for 3 doses as an initial loading procedure can reach a trough concentration of around 20 µg/L on the third day after commencement of teicoplanin therapy. Age, body weight, creatinine clearance, serum albumin concentration, and serum creatinine concentration can be factors that affect teicoplanin pharmacokinetic according to teicoplanin population pharmacokinetic analyses.11–13) However, Pea et al. reported by a multivariate analysis that the weight-adjusted dose (mg/kg), but not creatinine clearance or age, is the only significant factor that correlates with teicoplanin trough concentrations on the third day.10) Using multiple logistic regression analysis, we also previously showed that p values were 0.046 [odds ratio (OR): 0.91, 95% confidence interval (CI): 0.82–0.99] for body weight, 0.061 (OR: 1.02, 95% CI: 0.99–1.05) for creatinine clearance and 0.592 (OR: 1.42, 95% CI: 0.39–5.3) for serum albumin concentration, indicating that only the total dose per body weight statistically significantly affected teicoplanin pharmacokinetics.3) Thus, we recommend a loading dose of 11–15 mg/kg every 12 h for 3 doses, regardless of kidney function of ICU patients, to promptly achieve the new target of 15–30 µg/mL. However, creatinine clearance and serum albumin concentration cannot be excluded as factors fluctuating trough concentrations (Fig. 1). Further studies
in a larger number of patients are needed to improve the prediction accuracy of trough concentration.

It was reported that patients with a serum trough concentration >60 µg/mL had a higher incidence of elevated serum creatinine levels than those with concentrations of 20–40 µg/mL (p<0.05).14) Presterl et al.15) showed a moderate increase in liver enzymes during teicoplanin treatment. In this study, nephrotoxicity and hepatotoxicity were each observed in only one of 20 adult patients. It was shown that teicoplanin was a safe drug if trough concentrations were less than 30 µg/mL. Thus, we thought that a loading dose should be up to 15 mg/kg so as not to exceed 30 µg/mL of trough concentration. However, to see if a loading dose of 15 mg/kg is safe, a prospective study with an increased patient population would be needed.

Thompson16) suggested that nearly 10% of admissions to the general ICU will be MRSA-positive, of whom only half will be identified before discharge. With standard prevention, the risk of previously negative patients acquiring MRSA approximates to 1% per day in the first week and 3% per day thereafter, with nearly one-fifth progressing to bacteremia. MRSA remains the key issue for the ICU. On the other hand, Paul et al. showed that appropriate empirical antibiotic treatment had a significant survival benefit in MRSA bacteremia.17) In this study, there was no significant difference in trough concentrations between effective group (n=8, 17.4±6.1 µg/mL) and ineffective group (n=3, 20.3±7.5 µg/mL). Further studies in a larger number of patients are needed to investigate the relationship between the therapeutic effects and the trough concentration of teicoplanin. In the future, appropriate treatments for MRSA infections will lead to good outcomes in the ICU. For that purpose, an initial loading dose of 11–15 mg/kg every 12 h for 3 doses should be administered to promptly achieve the target trough concentration of 15–30 µg/mL on the third day after commencement of teicoplanin therapy in the ICU. Afterwards, individual maintenance dose adjustment to keep the target concentration (15–30 µg/mL) should be performed by therapeutic drug monitoring trough concentration simulation based on population pharmacokinetics and Bayesian estimation.

REFERENCES