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Rapid Attainment of Optimal Trough Concentrations in Organ Failure Mitigated by Teicoplanin

Shozo Yoshida[1], Hideshi Okada[1], Akio Suzuki[2], Keiko Suzuki[2,3], Takashi Niwa[2,3], Tomoaki Doi[1], Kunihiro Shirai[1], Kodai Suzuki[1], Yuichiro Kitagawa[1], Tetsuya Fukuta[1], Haruka Okamoto[1], Kazumasa Oda[1], Tomofumi Ohmori[2], Shiho Nakano[1], Michiyo Nakano[1], Takahiro Yoshida[1], Keisuke Kumada[1], Hiroaki Ushikoshi[1], Izumi Toyoda[1], Nobuo Murakami[3], Yoshinori Itoh[2] and Shinji Ogura[1]

1 Department of Emergency and Disaster Medicine, Gifu University Graduate School of Medicine, Gifu, Japan

2 Department of Pharmacy, Gifu University Hospital, Japan

3 Center for Nutrition Support & Infection Control, Gifu University Hospital, Gifu, Japan

Corresponding author: Hideshi Okada

hideshi@gifu-u.ac.jp

Department of Emergency and Disaster Medicine, Gifu University Graduate School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan.

Tel: 81582306448
Fax: 81582306451

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Abstract

The effective treatment of infections with teicoplanin requires an initial loading dose to reach optimal trough concentrations rapidly enough.

The optimal dosage of teicoplanin was previously established, and an optimal trough concentration of 15-20 μg/mL was assumed based on weight and estimated creatinine clearance. Teicoplanin treatment was performed with software-based monitoring of teicoplanin concentrations. We compared serum chemistry parameters and sequential organ failure assessment (SOFA) scores in patients with initial teicoplanin trough concentrations <15 μg/mL or ≥ 15 μg/mL (low- and high-concentration groups, respectively).

This study enrolled 29 patients (18 males, 11 females), including 4 patients receiving hemodiafiltration, who received initial teicoplanin injections between 2007 and 2010 at our hospital. Microbiological success rates did not differ significantly between the two groups, because additional teicoplanin was administered to patients whose initial trough concentrations were <15 μg/mL so as to attain this concentration. SOFA scores at 1 week post-treatment were significantly lower than those before treatment in the high-concentration group (before: 6.6 ± 3.8 vs. after: 5.3 ± 4.2, $p<0.05$), while there was no significant difference in the low-concentration group (before: 7.8 ± 3.8 vs. after: 7.5 ± 3.5, $p>0.05$).

Teicoplanin initial trough concentrations have been thought to contribute to improvement of organ failure. To maintain therapeutic concentrations of teicoplanin in patients with high disease severity, it was useful to ensure that initial trough values were ≥ 15 μg/mL. The initial dosage schedule of teicoplanin in emergency intensive care should consider disease severity.

Keywords: Teicoplanin; SOFA score; Intensive care

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Introduction

Teicoplanin is an antibiotic used in the treatment of serious infections caused by gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterococcus faecalis* [1]. The pharmacologic characteristics of teicoplanin include a long half-life (approximately 60 h) and large distribution capacity (approximately 1.2 L/kg) in comparison with vancomycin. Teicoplanin causes less nephrotoxicity and dermal toxicity than vancomycin, though there is no significant difference in efficacy between the two drugs [2-4].

The effective treatment of infections with teicoplanin requires an initial loading dose to rapidly reach optimal trough concentrations [5], which are considered to be 10-20 μg/mL for MRSA infections or over 20 μg/mL for deep-seated infections [6-10]. It was recently reported that fixed, high-dose loading of teicoplanin achieved the target therapeutic concentration of ≥ 15 μg/mL within 48 h of initial administration [11, 12]. On the other hand, poor clinical outcome was associated with trough concentrations <10 μg/mL [13].

Our previous study found that teicoplanin-monitoring software (TEICTDM v. 2.0; Astellas Pharma Inc., Tokyo, Japan), used to individually adjust the initial teicoplanin loading dose for each patient, was useful for attaining optimal concentrations (10-20 μg/mL) within 72 h after injection [14].

To demonstrate the importance of initial trough concentration, the present study compared sequential organ failure assessment (SOFA) scores [15], used to determine the extent of a person's organ function or rate of failure, and serum chemistry parameters in patients with initial teicoplanin trough concentrations <15 μg/mL or ≥ 15 μg/mL.

Patients and Methods

Ethical approval

This study was carried out in accordance with the guidelines for human studies adopted by the ethics committee of the Gifu University Graduate School of Medicine, and notified by the Japanese government (Institutional Review Board approval No. 21-153). In view of the retrospective nature of the study, subject's informed consent was not required.

Subjects

Patients under age 18 and those who were thermally injured were excluded from the study. After study approval was obtained from our local ethics committee, 29 patients (18 males, 11 females) including 4 patients receiving hemodiafiltration, with suspected or documented methicillin-resistant Staphylococcus aureus (MRSA) infections who had received teicoplanin injections at Gifu University Hospital from 2007 to 2010 were enrolled. All patients had received initial teicoplanin loading dose calculated using TEICTDM software, in which the target trough concentration on day 4 was set at 15-20 μg/mL [16, 17]. We compared serum chemistry parameters and sequential organ failure assessment (SOFA) scores in patients with initial teicoplanin trough concentrations <15 μg/mL or ≥ 15 μg/mL (low- and high-concentration groups, respectively). In patients whose initial trough concentrations did not reach 15 μg/mL, additional teicoplanin was administered to reach this concentration.

Drug dosing

TEICTDM software was used as previously described. The initial loading and maintenance doses of teicoplanin were established based on patient body weight and renal function and the target trough concentration on day 4 was set at 10-20 μg/mL [18]. Renal function was estimated based on creatinine clearance using the Jelliffe equation. Creatinine clearance in patients undergoing hemodiafiltration was in the 10-30 mL/min range.

Teicoplanin treatment, blood sampling, and analysis

Patients received the initial teicoplanin loading dose twice a day on the first and second days, followed by a maintenance dose once a day. Blood was drawn immediately before the injection of teicoplanin and was collected in a plastic vial containing ethylene glycol-bis (2-aminoethylether)-N,N,N′,N′-tetraacetic acid. Teicoplanin concentrations were determined by a fluorescence polarization immunoassay, according to the method of Rybak et al. using the teicoplanin reagent set (Oxis International Inc., Portland, OR) and an automated fluorescence polarization analyzer (TDx FLx; Abbott Japan Co. Ltd., Tokyo, Japan) [19]. The assay was performed in duplicate using TEICTDM software. The inter-assay coefficients of variation were 2.2%, 1.4%, and 1.0% at 10 μg/L, 35 μg/L, and 75 μg/L, respectively. The minimum detectable sensitivity of teicoplanin was 2.7 μg/mL. The effective measurement range of teicoplanin was 3.0 to 100.0 μg/mL.

Rates of microbiological and clinical success

Microbiological success was defined as the disappearance of bacteria from the site of infection during teicoplanin treatment, while clinical success was defined as the absence of infection relapse after completion of teicoplanin treatment.

Data analysis

Data were analyzed using SPSS version 11 (SPSS Inc., Chicago, IL). Parametric variables were analyzed using the Fisher exact probability test, Mann-Whitney U test, unpaired t-test, Wilcoxon test, and Yates' chi square test. A p-value of <0.05 was considered statistically significant.

Results

Patient profiles before treatment

Table 1 summarizes patients' clinical data before treatment, comparing the low- and high-concentration groups. There were no significant differences between the two groups in age, body weight, white blood cell count, SOFA score, or concentrations of albumin, aspartate aminotransferase, alanine aminotransferase, creatinine, and C-reactive protein **(Table 1)**. The percentage of patients undergoing hemofiltration was also similar in both groups. There was no significant difference in the duration of treatment between the low- and high-concentration groups (16.1 ± 12.8 days vs. 17.7 ± 11.2 days, respectively; p>0.05)

Initial trough concentrations and SOFA scores

Microbiological success rates were not significantly different between the two groups at 1 week after injection **(Figure 1)**. Similarly, the groups did not differ significantly in terms of pre-treatment SOFA scores (low-concentration group: 7.8 ± 3.8 vs. high-concentration group: 6.6 ± 3.8, p>0.05). In the high-concentration group, SOFA scores were significantly higher before treatment than at 1 week after treatment (before: 6.6

± 3.8 vs. after: 5.3 ± 4.2, p< 0.05). In contrast, there was no significant difference in the low-concentration group (before: 7.8 ± 3.8 vs. after: 7.5 ± 3.5, p>0.05).

To determine which components of the SOFA score had improved, SOFA score variables were investigated in both groups **(Table 2)**. None of variables differed significantly before and after treatment.

Discussion

Several previous reports have shown that an initial loading dose of teicoplanin is required to obtain favorable clinical outcomes by achieving an optimal trough concentration [8-10, 13], and it is recommended that this concentration be achieved using TDM [12, 20, 21]. It was reported that fixed, high-dose loading of teicoplanin achieved the target therapeutic range of ≥ 15 μg/mL within 48 h of the start of administration [11, 12]. Therefore, in the present study, 15 μg/mL of teicoplanin was set as the target initial trough value.

Table 1 Patient profiles before treatment. MRSA: Methicillin-Resistant *Staphylococcus aureus*; MRSE: Methicillin-Resistant *Staphylococcus epidermidis*; *E. faecium*: *Enterococcus faecium*; *S. capitis*: *Staphylococcus capitis*; Unknown: Although culture was negative, the physicians suspected MRSA infection and decided to continue the teicoplanin treatment.

	Initial Trough Concentration ≥ 15 μg/ml	<15 μg/ml	
	n=14	n=15	P
Sex (Male/Female)	8/6	10/5	0.612[1]
Age	64 (23-83)	74 (27-88)	0.097[2]
Body Weight (kg)	63.0 ± 14.2	60.2 ± 13.0	0.578[3]
Albumin (g/dL)	2.6 ± 0.5	2.3 ± 0.4	0.197[3]
AST (IU/L)	31.8 ± 19.6	37.7 ± 20.1	0.413[3]
ALT (IU/L)	31.1 ± 18.8	28.7 ± 21.2	0.521[3]
Creatinine (g/dL)	1.0 ± 0.6	1.0 ± 1.1	0.985[3]
CRP (mg/dL)	8.9 ± 7.2	13.9 ± 6.9	0.086[3]
White Blood Cell (/mL)	9197.9 ± 3765.3	14267.3 ± 10072.5	0.088[6]
SOFA score	6.6 ± 3.8	7.8 ± 3.8	0.456[2]
Hemofiltration (+/-)	2/12	2/13	0.674[1]
The duration of Treatment (Days)	17.7 ± 11.2	16.1 ± 12.8	0.363[3]
Pathogen			
MRSA	2	9	
MRSE	6	4	
E. facium	2	2	
S. capitis	2	0	
Unknown (Culture negative)	2	0	
The site of Positive culture			
Blood	9	7	
Lung	0	3	
Peritonotis	2	3	
Wounded Area	2	2	
Mediastinitis	1	0	

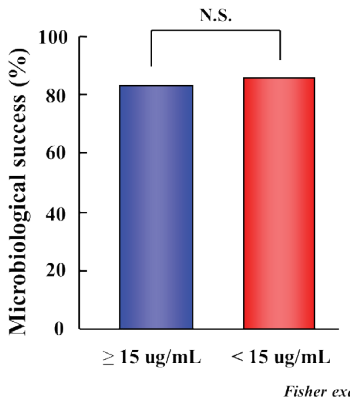

Figure 1 Microbiological success rates at 1 week after TEIC injection. There was no significant difference between patients with initial trough concentrations <15 μg/mL and those with concentrations ≥ 15μg/mL.

In this study, additional teicoplanin was administered to patients whose initial trough concentrations were <15 μg/mL. This resulted in similar microbiological success rates in both the low- and high-concentration groups at 1 week after injection, although SOFA scores were significantly different at the two time points in the high-concentration group. These results suggest that initial trough concentration contributes to the amelioration of organ failure. Further, it was important not only to reach an initial trough value of 15 μg/mL, but also to reach it rapidly.

It has been thought that changes in teicoplanin trough values are influenced by variations in teicoplanin distribution due to aging, disease severity, and presence or absence of blood purification therapy. To effectively achieve the desired serum teicoplanin concentrations in patients with severe disease, it is important to attain an initial trough value of 15 μg/mL. Indeed, the Surviving Sepsis Campaign guidelines recommended that effective intravenous antimicrobials should be administered within 1 h of the recognition of septic shock as well as severe sepsis without septic shock [22]. Thus, in the seriously ill patients in this study it was necessary to consider the disease severity, including the SOFA score, before teicoplanin administration. Our findings suggested that an adequate initial teicoplanin loading dose was required to achieve improvement in SOFA scores after teicoplanin administration.

SOFA scores improved less in patients whose initial trough concentrations did not reach 15 μg/mL, most likely for two reasons: 1) these patients were older and thus disease severity was higher, and 2) enough initial trough values were not provided. In the high-concentration group, which did attain trough values of ≥ 15 μg/mL, SOFA score variables did not improve significantly after teicoplanin treatment, although respiratory and cardiovascular variables did show marginal differences. This finding regarding the specific variables affected suggests that initial trough values influenced the body as a whole but not specific organs.

Teicoplanin is excreted mainly in the urine, and its elimination half-life in adult volunteers has been reported to range between

Table 2 Comparison of SOFA variables between patients with initial TEIC trough concentrations <15 μg/mL and those with concentrations ≥ 15 μg/mL. Parametric variables were analyzed using the Wilcoxon test.

Initial Trough Concentration						
	≥ 15 μg/mL (n=14)			<15 μg/mL (n=15)		
Variables	**Before**	**1 week after**	**p**	**Before**	**1 week after**	**p**
Respiratory	2.7 ± 0.8	2.1 ± 15	0.077	2.7 ± 1.0	2.6 ± 0.9	0.683
Coagulation	0.6 ± 0.9	0.5 ± 0.9	0.655	0.7 ± 0.9	0.8 ± 0.8	0.480
Liver	0.5 ± 0.8	0.6 ± 0.9	0.564[3]	1.5 ± 1.0	1.7 ± 1.5	0.206
Cardiovascular	1.0 ± 13	0.5 ± 0.9	0.161	1.1 ± 1.4	0.7 ± 1.0	0.276
Central Nerve System	1.0 ± 1.7	1.0 ± 1.7	I .000	0.9 ± 1.2	0.9 ± 1.2	1.000
Renal	0.8 ± 1.4	0.6 ± 1.4	0.320	1.0 ± 1.7	0.7 ± 1.5	0.317
Total	6.6 ± 3.8	5.3 ± 4.2	0.032	7.83 ± 3.8	7.5 ± 3.5	0.661

Wilcoxon test

50 and 168 h depending on the duration of sample collection, supporting its once-daily dosage recommendations [16, 17]. Therefore, it is often difficult to achieve optimal teicoplanin concentrations even in patients with normal renal function.

In conclusion, this study showed that rapid attainment of optimal teicoplanin trough concentrations was very important for achieving higher SOFA scores, although there were no significant differences in the sub scores of its variables. This result suggested that rapid attainment of optimal teicoplanin trough concentrations improved the general condition of critically ill patients. Hence, planning initial teicoplanin dosage schedules in the context of emergency intensive care should take into consideration each patient's disease severity and treatment regimen.

Study Limitation

The limitations of this study include small sample size. Further investigation is required.

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