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Short communication

Evaluation of teicoplanin concentrations and safety analysis in neonates

Takaaki Yamada [a], Toshio Kubota [a,b,*], Masako Nakamura [b], Masayuki Ochiai [c], Mahoro Yonezawa [b], Takahisa Yano [a], Takehiro Kawashiri [a], Nobuaki Egashira [a,d], Toshiro Hara [c], Satohiro Masuda [a,d]

[a] Department of Pharmacy, Kyushu University Hospital, Fukuoka, Japan
[b] Department of Clinical Pharmacy and Pharmaceutical Care, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan
[c] Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[d] Department of Clinical Pharmacology and Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka, Japan

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ABSTRACT

The aims of this study were (i) to evaluate the relationship between teicoplanin (TEIC) dosage and subsequent trough concentration, (ii) to investigate factors that affect TEIC serum concentration fluctuations and (iii) to examine the association between serum concentration of TEIC and adverse reactions in neonates. A total of 37 eligible neonates (<28 days of age) treated with TEIC from 2008–2012 were included in this study. The median trough concentration in the loading dose regimen of >12–16 mg/kg on Day 1, followed by >6–8 mg/kg every 24 h (q24 h) was 19.6 μg/mL on Day 3 or 4, and the median trough concentration in the maintenance dose regimen of >6–8 mg/kg q24 h was 18.5 μg/mL at steady-state. There were significant correlations between serum creatinine and concentration/dose (C/D) ratio ($r = 0.475$, $P = 0.019$), body weight and C/D ratio ($r = -0.425$, $P = 0.038$) and corrected gestational age and C/D ratio ($r = -0.482$, $P = 0.017$) after administering the loading dose. The incidence of hepatic dysfunction, renal impairment and thrombocytopenia was 14.8%, 20.0% and 14.8%, respectively. There was no significant difference in the incidence of adverse reactions between the trough concentration <20 μg/mL and ≥20 μg/mL groups. These data suggest that the recommended TEIC dosage for neonates is appropriate to achieve and maintain a trough concentration range of 15–30 μg/mL, and it is possible to set the target trough concentration at ≥20 μg/mL for deep-seated infections such as endocarditis, bone and joint infections, and osteomyelitis.

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1. Introduction

Infection with meticillin-resistant *Staphylococcus aureus* (MRSA) significantly increases morbidity and mortality in neonatal intensive care units. Thus, prompt treatment with appropriate antimicrobial agents using adequate dosage regimens is required [1].

Teicoplanin (TEIC), a glycopeptide antibiotic, has been used to treat MRSA infections. Since TEIC has a long elimination half-life, an initial loading dose is required to rapidly achieve the optimal exposure, correlating well with its area under the concentration–time curve and trough concentration. Therapeutic drug monitoring (TDM) is recommended for use of TEIC during anti-MRSA therapy to ensure adequate trough concentrations. It is commonly considered that the trough concentration of TEIC should be ≥10 μg/mL for MRSA infections and ≥20 μg/mL for deep-seated infections such as endocarditis, bone and joint infections, and osteomyelitis [2,3]. Recently, it has been reported that it is necessary to achieve a trough concentration of ≥15 μg/mL to obtain the high clinical efficacy of TEIC for MRSA infections, and 15–30 μg/mL has been recommended as the new target trough range [4].

In the Martindale drug reference [5], it is recommended that TEIC is administered intravenously at 16 mg/kg as a loading dose on Day 1, followed by a daily maintenance dose of 8 mg/kg in neonates. However, there are limited data regarding dosage and

* Corresponding author. Present address: Department of Clinical Pharmacy and Pharmaceutical Care, Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Tel.: +81 92 642 6573; fax: +81 92 642 6647.
E-mail addresses: t-kubota@pharm.med.kyushu-u.ac.jp, t-kubota@med.kyushu-u.ac.jp (T. Kubota).

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subsequent trough concentrations of TEIC in neonates [6], and there are no data on whether the recommended loading and maintenance doses for neonates reach the target trough range (15–30 μg/mL) as a surrogate marker for the anti-MRSA efficiency of TEIC.

It has been shown that nephrotoxicity and hepatotoxicity were caused at a TEIC trough concentration of >60 μg/mL, and that thrombocytopenia was found at a trough concentration of >40 μg/mL in adult patients treated with TEIC [7,8]. Thus, the safety of TEIC at a trough concentration of ≥20 μg/mL has been confirmed in adult patients [9]. However, there are few reports regarding the adverse reactions in neonates treated with TEIC [6]. Moreover, the safety of TEIC in neonates with a trough concentration of ≥20 μg/mL is still unclear. In this study, we evaluated the relationship between TEIC dosage and subsequent trough concentration in neonates and investigated the factors that affect the fluctuation of TEIC serum concentrations. Moreover, we examined the incidence of adverse reactions in neonates treated with TEIC and evaluated the safety of TEIC in neonates with a trough concentration of ≥20 μg/mL.

2. Methods

2.1. Patients

Of 54 neonates (<28 days of age) who received TEIC from October 2008 to December 2012 at Kyushu University Hospital (Fukuoka, Japan), a total 43 eligible neonates who underwent at least one serum TEIC concentration measurement were included in this study. Three neonates who were treated with TEIC for <3 days or >28 days were excluded. According to the criteria for the safety evaluation of antimicrobial agents [10], three neonates with severe hepatic dysfunction [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) at >5× the upper limit of normal (ULN)] or renal impairment [serum creatinine (SCr) at >2× ULN] before TEIC administration were also excluded. Finally, of 43 neonates, 37 were entered into this study. All data were retrospectively collected from electronic charts and patient characteristics were summarised.

2.2. Teicoplanin assay

Serum TEIC concentrations were determined using a fluorescence polarisation immunoassay system (TDx FLx analyzer; Abbott Japan Co. Ltd., Tokyo, Japan). The within- and between-run coefficient of variation was <7% for concentrations ranging between 5 μg/mL and 100 μg/mL, with a limit of quantification of 2 μg/mL [11].

2.3. Teicoplanin dosage and subsequent trough concentration

TEIC trough concentrations were divided into two groups: trough concentration after the loading dose and trough concentration after the maintenance dose. For the loading dose analysis, 24 patients with a trough concentration measured just before administration on Days 3 or 4 were enrolled. For the maintenance dose analysis, 26 patients with a trough concentration that was expected to reach a steady-state were enrolled. Steady-state was defined as the condition when the TEIC dosage was not changed for ≥72 h based on its half-life in paediatric patients [12].

2.4. Safety analysis of teicoplanin

AST, ALT, SCr and platelet (PLT) levels were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0. During the period of TEIC administration, adverse reactions of grade 2 or higher according to CTCAE (AST or ALT at >3× ULN, SCr at >1.5× baseline and PLT at <75 000 μL^{-1} on at least two consecutive measurements) were defined as hepatic dysfunction, renal impairment and thrombocytopenia, respectively [10]. Patients with no laboratory values before and during TEIC administration were excluded from the safety analysis. In addition, seven patients with more than grade 2 thrombocytopenia before TEIC administration were excluded from the analysis of thrombocytopenia. Finally, 27, 25 and 27 neonates were recruited in the evaluations of hepatic function, renal function and thrombocytopenia, respectively. TEIC trough concentration was divided into <20 μg/mL and ≥20 μg/mL groups, and the incidence of hepatic dysfunction, renal impairment and thrombocytopenia were compared. When the trough concentration reached ≥20 μg/mL at least once, it was defined as the ≥20 μg/mL group. When the adverse reaction occurred before the trough level reached ≥20 μg/mL, it was defined as the <20 μg/mL group.

2.5. Statistical analyses

Spearman's correlation analysis was performed to evaluate relationships between dose and trough concentration, SCr and concentration/dose (C/D) ratio, body weight and C/D ratio, corrected gestational age at the time of TEIC treatment and C/D ratio, and postnatal age and C/D ratio. The incidence of adverse reactions in neonates treated with TEIC was compared between the trough concentration <20 μg/mL and ≥20 μg/mL groups using Fisher's exact test. All analyses were performed using JMP software v.9.0.2 (SAS Institute Inc., Cary, NC). P-values of <0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

There were 23 males and 14 females. The median (range) values were as follows: gestational age, 30 weeks and 3 days (22 weeks and 6 days–40 weeks and 5 days); birth weight, 1704 g (502–2995 g); postnatal age when TEIC was injected, 14 days (0–28 days); corrected gestational age, 32 weeks and 4 days (22 weeks and 6 days–42 weeks and 6 days); duration of TEIC administration, 11 days (3–25 days); AST, 24.5 U/L (10–99 U/L); ALT, 9 U/L (2–40 U/L); SCr, 0.60 mg/dL (0.12–1.48 mg/dL); and PLT, 183 000 μL^{-1} (23 000–634 000 μL^{-1}). Of 37 neonates, 35 were concomitantly administered carbapenems or cephalosporins. Two neonates received fluconazole concomitantly with TEIC and other antibiotics.

3.2. Loading dose and subsequent trough concentration

Table 1 shows the median TEIC trough concentrations and the number of neonates achieving a trough concentration of ≥15 μg/mL on Day 3 or 4 divided into each loading dose regimen. In the loading dose regimen of >12–16 mg/kg on Day 1, followed by >6–8 mg/kg every 24 h (q24 h), the median trough concentration was 19.6 μg/mL. The percentage achieving the trough concentration of ≥15 μg/mL in neonates who received >12 mg/kg on Day 1, followed by >6 mg/kg q24 h was 70.0% (7/10), whilst that in neonates who received ≤12 mg/kg on Day 1, followed by ≤6 mg/kg q24 h was 42.9% (6/14).

To examine the factors that affect the fluctuation of TEIC serum concentrations, correlation analyses were performed (Fig. 1). There were significant correlations between cumulative dose at Day 3 or 4 and trough concentration ($r = 0.724$, $P < 0.001$),

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