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Therapeutic Drug Level Monitoring of Teicoplanin in Korean Pediatric Patients with Normal versus Impaired Renal Function

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ABSTRACT

Background: Teicoplanin is used to treat serious gram-positive infections. Optimal teicoplanin trough levels are considered to be ≥ 10 μg/mL. Despite its wide use in various clinical settings, data on teicoplanin trough level in pediatric patients are limited. Therefore, the aim of this study was to investigate the therapeutic drug level monitoring of teicoplanin in Korean pediatric patients, including those with impaired renal function.
Methods: A retrospective study was performed in pediatric patients (age ≤ 18 years old) who received teicoplanin from September 2014 to April 2018. The regimen included a loading dose of 10 mg/kg/dose at 12 hours' interval three times in a row, and a maintenance dose of 10 mg/kg/dose commenced at 24 hours of interval after the loading dose, with a maximum of 400 mg/dose, respectively. The first therapeutic drug levels were measured. Distribution and characteristics of trough levels in patients with decreased renal function and those with bacteremia were also assessed.
Results: A total of 187 trough levels were collected from 143 patients. Hematologic and oncologic diseases were the most common underlying diseases (83.2%, n = 119). One hundred eighty trough levels were first measured, and their median value was 16.2 μg/mL (range, 2.3–100 μg/mL) and the median interval between initial teicoplanin injection and 1st trough level was 96.5 hours (range 47.6–179.3 hours). Lower steady-state levels were observed in younger age group (median, 13.5 vs. 18.0 μg/mL, $P = 0.038$). Median trough levels were higher in patients with decreased renal functions ($P < 0.001$). In addition, among eight with gram-positive bacteremia, seven of them had a favorable outcome.
Conclusion: This study provides additive information on trough level monitoring of teicoplanin in children with impaired renal function and treatment effect in patients with gram-positive bacteremia. Careful monitoring for steady state trough levels of teicoplanin is warranted.

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Keywords: Teicoplanin; Therapeutic Drug Level Monitoring; Children; Impaired Renal Function; Bacteremia

INTRODUCTION

Since its first isolation from *Actinoplanes teichomyceticus* in 1970s, teicoplanin has become one of the widely used glycopeptides along with vancomycin for treating gram-positive bacterial infections.[1] Compared to vancomycin, teicoplanin has several advantages, including a lower incidence of adverse events like nephrotoxicity and longer half-life, allowing once-daily bolus injection.[2-4]

In general, optimal trough plasma levels of teicoplanin for treatment have been considered to be at least 10 μg/mL, although trough levels of 20–60 μg/ml are permissive for severe staphylococcal infections including endocarditis and bone-and-joint infection.[5] Trough levels over 60 μg/mL are known to be associated with adverse effects such as nephrotoxicity.[6,7]

Despite its wide use in various clinical settings, data on teicoplanin trough level in pediatric patients are limited. The aim of this study was to demonstrate the therapeutic drug level monitoring of teicoplanin in Korean pediatric patients including ones with impaired renal function, and its treatment effect for gram-positive bacteremia.

METHODS

Data source and patient selection

Trough levels of teicoplanin in pediatric inpatients 18 years old or younger at Samsung Medical Center, Sungkyunkwan University School of Medicine between September 2014 and April 2018 were collected. Medical records were retrospectively reviewed to collect clinical information. Distribution and characteristics of trough levels in patients with decreased renal function and those with bacteremia were also assessed. Patients who were included in this study were 18 years old or younger who received teicoplanin for at least 4 doses and had available exam data of trough levels. Process of data exclusion is described in **Supplementary Fig. 1**.

The authors defined decreased renal function as estimated glomerular filtration rate (eGFR) less than 70 mL/min/body surface area (BSA),[8] which was calculated with modified Schwartz equation (K × height in centimeter/plasma creatinine [mg/dL], K = 0.413).

Within bacteremia population, patients were regarded to be at defervescence if body temperature lower than 37.5°C was achieved for at least 48 hours.

Administration and drug level monitoring of teicoplanin

Teicoplanin was administered intravenously. Study population received teicoplanin at a loading dose of 10 mg/kg/dose at 12 hours' interval, three times in a row. Maintenance dose was commenced at a dose of 10 mg/kg/dose 24 hours after the last loading dose. The maximal dose of administered teicoplanin was 400 mg. Trough levels of teicoplanin were measured with liquid chromatography-tandem mass spectrometry method at the Department of Laboratory Medicine and Genetics of the Samsung Medical Center. Detailed information on standard materials used, preparations of calibrators, quality controls, instrumental condition, and method validation were described in a previous study.[9]

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Steady state sample was defined as the one collected after the fourth or fifth dose of teicoplanin. Drug levels were measured within seven days from the initial dose after reaching steady state in this study. Each of the episodes were considered to be separate if a duration between the last dose of previous teicoplanin and the first dose of restart is 5 days or more.

Statistical analysis

Descriptive data are expressed as median and ranges. The χ^2 test and Mann-Whitney U test were used to compare categorical and continuous variables, respectively. Differences in the achievement of target trough level (≥ 10 μg/mL) were evaluated for statistical significance with logistic regression models. Patient age, sex, body weight, serum creatinine, eGFR, interval between initial dose and 1st steady state exam, loading and maintenance doses were included as covariates. Analyses were done with IBM SPSS Statistics, version 25 (SPSS Inc., Chicago, IL, USA). Statistical significance was defined by a two-sided *P* value < 0.05.

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. 2018-08-045). Informed consent was waived because this study was retrospective, and measurement of serum teicoplanin drug level was a routine process for patient care.

RESULTS

Patient characteristics

A total of 187 trough levels were collected from 143 patients (**Table 1**), including 74 (51.7%) males. The median age of all patients was 6.2 years (range, 0.09–17.7 years). Hematologic and oncologic diseases were the most common underlying diseases (n = 119, 83.2%), followed by gastroenterologic and hepatologic disease (n = 6, 4.2%), primary immunodeficiencies (n

Table 1. Patients' characteristics

Characteristics	Values
Total No. of patients	143
Sex, male	74 (51.7)
Median age, yr	6.2 (0.09–17.7)
Median body weight, kg	20.8 (4.47–79.8)
Underlying disease	
Hematology/oncology	119 (83.2)
Primary immunodeficiency	5 (3.5)
Gastroenterology/hepatology	6 (4.2)
Neurology	3 (2.1)
Cardiology	3 (2.1)
Others[a]	7 (4.9)
Reason for treatment	
Targeted therapy	9 (6.3)
Gram positive bacteremia	8 (5.6)
Skin infection	1 (0.7)
Empiric therapy	134 (93.7)
Neutropenic fever	108 (75.5)
Pneumonia	17 (11.9)
Osteomyelitis or arthritis	7 (4.9)
Skin infection	2 (1.4)
Median duration of use, day	7.4 (4.1–33.3)

Values are presented as number (%) or median (range).
[a]Chronic kidney disease (n = 1), chronic pneumonitis of infancy (n = 1), lymphangioma (n = 3), myopathy (n = 1), infantile myofibromatosis (n = 1).

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= 5, 3.5%), neurologic disease, and cardiologic diseases (n = 3, 2.1% respectively). The most common reason of teicoplanin use was empiric treatment for prolonged neutropenic fever in hematologic and oncologic disease (n = 143, 75.5%).

Teicoplanin trough levels

Among 187 measured trough levels, 180 were first-measured-values. The median value of 1st measured trough levels was 16.2 μg/mL (range, 2.3–100 μg/mL). Interval between initial teicoplanin injection and 1st trough level ranged from 47.6 hours to 179.3 hours and median was 96.5 hours. Data were divided into two groups based on trough levels: trough level < 10 μg/mL (n = 44, 24.4%) and trough level ≥ 10 μg/mL (n = 136, 75.6%). There were 77 data (42.8%) of which trough levels were between ≥ 10 μg/mL to < 20 μg/mL and 55 data (30.6%) for ≥ 20 μg/mL to < 60 μg/mL. Four trough levels (2.2%) were over 60 μg/mL which is generally considered as toxic level. Characteristics of these patients are described in **Supplementary Table 1**. Patients whose steady state trough level was less than 10 μg/mL tended to be younger, have lower body weight, have longer interval between the 1st injection and trough level measurement, and have better kidney function (**Table 2**). Patients were also divided into two groups based on age: patients < 6 years old (infants and young children) vs. patients ≥ 6 years old (school-aged children and adolescents). Although trough levels in both groups were within optimal therapeutic range, lower steady state levels were observed in the younger age group (median: 13.5 vs. 18.0 μg/ml, $P = 0.038$). In a logistic regression model, patients whose trough levels were within target range tended to have higher body weight, shorter interval between initial injection and trough level measurement, lower eGFR, higher maintenance dose (**Supplementary Table 2**).

Patients with decreased renal function vs. normal renal function

Eight patients had decreased renal function (median eGFR: 62.6 mL/min/BSA, range: 43.8–66.5 mL/min/BSA). Of these patients, four received renal replacement therapy including one patient who had received both peritoneal dialysis and continuous renal replacement therapy (**Table 3**).

Median trough levels at steady-state were significantly higher in this group with decreased renal function than in patients with normal renal function (median trough level: 49.1 vs. 15.6

Table 2. Comparison of characteristics by teicoplanin trough levels

Characteristics	< 10 μg/mL (n = 44)	≥ 10 μg/mL (n = 136)	*P* value
Age, yr	5.4 (0.3–17.1)	7.2 (0.1–17.7)	0.041[a]
< 6	25 (56.8)	56 (41.2)	
6–13	15 (34.1)	49 (36.0)	
≥ 13	4 (9.1)	31 (22.8)	
Sex, male	20 (45.5)	71 (49.3)	0.436[b]
Body weight, kg	17.3 (5.6–62.7)	21.8 (4.5–79.8)	0.027[a]
< 15	21 (47.7)	40 (29.4)	
15–30	13 (29.6)	41 (30.1)	
30–45	6 (13.6)	25 (18.4)	
≥ 45	4 (9.1)	30 (22.1)	
Interval between initial dose and 1st steady state exam, hr	107.8 (47.7–167.7)	96.0 (62.2–179.3)	0.048[a]
eGFR, mL/min/BSA	203.5 (85.0–395.1)	144.4 (43.8–384.6)	< 0.001[a]
Loading dose, mg/kg	9.7 (6.4–11.0)	9.7 (3.6–12.8)	0.647[a]
Maintenance dose, mg/kg	9.7 (5.3–11.0)	9.7 (3.6–12.8)	0.960[a]
Underlying hematology/oncologic disease	32 (72.7)	123 (85.4)	0.003[b]

Values are presented as number (%) or median (range).
eGFR = estimated glomerular filtration rate, BSA = body surface area.
[a]Mann-Whitney U test; [b]χ^2 test.

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Table 3. Normal vs. impaired renal function[a]

Characteristics	Normal renal function (n = 172)	Impaired renal function (n = 8)	*P* value
Sex, male	88 (51.1)	5 (62.5)	0.742[b]
Age, yr	6.4 (0.1–17.7)	9.82 (2.7–16.0)	0.207[c]
Body weight, kg	21.0 (4.5–79.8)	26.2 (12.4–62.7)	0.309[c]
Median eGFR, mL/min/1.73 m^2	161.6 (70.6–395.1)	62.6 (43.8–66.5)	< 0.001[c]
Median trough levels of teicoplanin, μg/mL	15.6 (2.3–100.0)	49.1 (26.0–65.8)	< 0.001[c]
Trough levels, μg/mL			
< 20	121 (70.3)	-	-
20–60	48 (27.9)	7 (87.5)	< 0.001[b]
≥ 60	3 (1.7)	1 (12.5)	< 0.001[b]
Renal replacement therapy			
Peritoneal dialysis	-	2 (25.0)	-
Continuous renal replacement therapy	-	3 (37.5)	-
Median interval between initial dose and steady state exam, hr	96.5 (47.7–179.3)	108.0 (70.6–169)	0.767[c]

Values are presented as number (%) or median (range).
eGFR = estimated glomerular filtration rate.
[a]eGFR less than 70 mL/min/1.73 m^2; [b]χ^2 test; [c]Mann-Whitney U test.

μg/mL, *P* < 0.001) (**Fig. 1**). All trough levels at steady-state in these patients were over 20 μg/mL. One patient showed trough level over 60 μg/mL. Compared to patients with normal renal function, patients with decreased renal function showed no statistical differences in loading dose, maintenance dose, or interval between the initial dose and measurement of trough level.

Patients with gram positive bacteremia

Eight patients had gram-positive bacteremia in the study population (**Table 4**). All patients with gram-positive bacteremia had normal renal function (median eGFR: 147.7 mL/min/BSA, range, 98.0–209.0 mL/min/BSA). Median trough level at steady-state was 11.2 μg/mL (range, 8.2–19.3 μg/mL). Three patients failed to reach optimal trough level even at steady-state after five to seven doses of teicoplanin. *Staphylococcus aureus* was the most common pathogen (n = 4, 50%), followed by *Viridans streptococci* (n = 2, 25%) and *Enterococcus gallinarum* (n = 1) or coagulase negative staphylococci (n = 1). These eight isolates were sensitive to teicoplanin (n = 6) or vancomycin (n = 7).

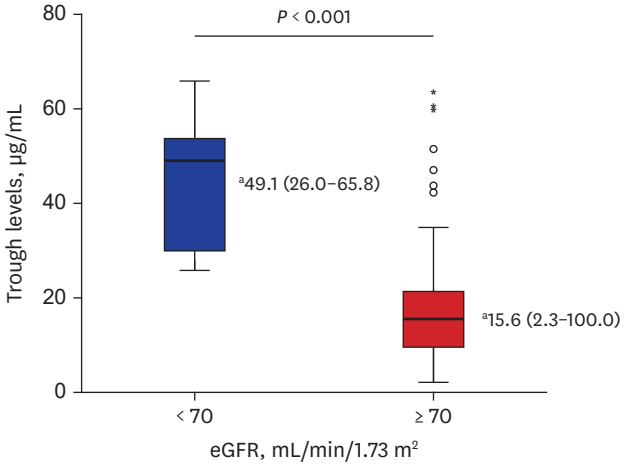

Fig. 1. Steady state trough levels: decreased vs. normal renal function.
Differences in steady state trough levels between patients with decreased renal function and those with normal renal function. Decreased renal function was defined as eGFR less than 70 mL/min/BSA, calculated with modified Schwartz equation.
BSA = body surface area, eGFR = estimated glomerular filtration rate.
[a]Median (range).

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Table 4. Patients with gram positive bacteremia

Patient No.	1	2	3	4	5	6	7	8
Age, yr	1.1	5.8	4.4	6.9	11.2	0.5	6.5	14.9
Sex	F	M	M	M	F	M	M	M
Underlying disease	RBL	TOF	WAS	MTT	ALL	AML	None	Burkitt lymphoma
Trough level, μg/mL	8.2	8.8	9.2	12.3	11.1	11.3	18.5	19.3
eGFR, mL/min/1.73 m^2	128.4	98.0	209.0	162.0	167.0	116.3	133.4	101.1
Pathogen	CoNS	*Enterococcus gallinarum*	*Viridans Streptococci*	*Viridans Streptococci*	*S. aureus*	*S. aureus*	*S. aureus*	*S. aureus*
MIC, teicoplanin	S (≤ 0.5)	S (≤ 0.5)	N/A	N/A	S (≤ 0.5)	S (≤ 0.5)	S (≤ 0.5)	S (≤ 0.5)
MIC, vancomycin	S (≤ 0.5)	R (4)	S (0.25)	S (0.25)	S (1)	S (1)	S (1)	S (1)
Type of central venous catheter	Chemoport	No	Hickmann	Hickmann	Hickmann	Hickmann	No	Chemoport
Count of culture-positive lumen	1	N/A	3	2	2	1[a]	N/A	1
Concurrent peripheral culture positive	No	Yes	Yes	Yes	Yes	No[a]	Yes	Yes
Clinical outcomes								
Defervescence within 2 days	Yes	Yes	Yes	No	No	No	No	Yes
Follow-up culture	Positive	Positive	Negative	Negative	Negative	Positivea	Negative	Negative
Culture negative within 3 days	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Duration of bacteremia, day	6	3	2	1	1	2	2	1
Microbiological cure at 14 days	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Mortality in 30 days	No	N/A	No	No	No	No	N/A	No

RBL = retinoblastoma, TOF = tetralogy of Fallot, WAS = Wiskott-Aldrich syndrome, MTT = malignant triton tumor, ALL = acute lymphoblastic leukemia, AML = acute myelogenous leukemia, eGFR = estimated glomerular filtration rate, CoNS = coagulase-negative *Staphylococci*, *S. aureus* = *Staphylococcus aureus*, MIC = minimal inhibitory concentration, S = sensitive, R = resistant, N/A = not available.
[a]From follow-up blood culture performed within 24 hours, organism was reported in two central lumens with peripheral blood culture concurrently.

In seven patients (except patient 1), blood culture became negative within three days from the initial blood culture. All the patients reached microbiological cure within 14 days. Defervescence was achieved within a median of 4.5 days (range, 2–13 days). In three patients who did not reach target trough level (patient number: 1, 2, and 3), bacteremia resolved by 14 days, although patient 1 had persistent bacteremia for 3 days.

Four patients had changes in their initial antibiotic agents during treatment. Two patients had change of teicoplanin to vancomycin. One patient (patient 6) had this change of antibiotics because he developed *S. aureus* bacteremia while he was receiving teicoplanin as an empirical therapy for neutropenic fever. One patient (number 5) started teicoplanin when she developed *S. aureus* bacteremia. She received teicoplanin for 5 days. After that, she had vancomycin for continuation. Two patients (patient number: 2 and 7) had change of vancomycin to teicoplanin due to adverse reaction to vancomycin (drug rash and drug fever, respectively) and achieved cure for the bacteremia.

DISCUSSION

This study provides information on the pharmacokinetics of teicopalnin in pediatric patients with decreased renal function. In addition, in a subset of patients with gram-positive bacteremia, teicoplanin showed favorable treatment effect. Although the number is low, this observation would be helpful for physicians in the field when prescribing teicoplanin in high-risk pediatric patients with a wide range of age, variable renal functions, and serious invasive bacterial infection.

Pharmacokinetics of teicoplanin has been steadily studied in various clinical settings, including adult patients,[5,10-13] pediatric patients,[14-20] and patients with hematologic

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malignancies.[21-25] A number of studies on the pharmacokinetics of teicoplanin have shown a common problem that the therapeutic range of trough level is not achieved early and occasionally not reached even at steady state. To overcome this problem, the need of loading dose has been suggested.[3,5,26] Chae et al.[27] have demonstrated that the proportion of trough levels achieving ≥ 10 mg/L is only 20% (days 3–5) or 38% (days 6–8) in the standard dose group. Nah et al.[12] have reported that patients with sub-optimal (< 10 mg/L) plasma teicoplanin concentrations constituted nearly half of their total study population. The majority of these patients received the recommended loading dose (three doses of 400 mg administered every 12 hours). Kim et al.[11] have reported that a high loading dose regimen (≥ 9 mg/kg) was associated with adverse events during treatment. To weigh the balance between optimal treatment efficacy and increased risk of adverse events, therapeutic drug monitoring is necessary in these critically ill patients who require teicoplanin treatment.[6,12,13,27]

This issue becomes more complicated in pediatric settings due to a higher clearance in younger children which leads to age-related differences in serum teicoplanin levels. In early studies, Reed et al.[17] enrolled twelve infants and children and Sanchez et al.[18] recruited twenty-one critically ill children and measure teicoplanin drug levels. They did not observe any statistical differences in mean serum concentration or pharmacokinetic characteristics among different age groups. Strenger et al.[19] performed a large-scale study and analyzed 1,357 samples in 280 patients and reported that toddlers (1.0–5.9 years) had significantly lower trough levels of teicoplanin, with a 2-fold higher risk of suboptimal level (< 10 mg/L). We also observed an age-related difference in trough levels at steady state when comparing two age groups (< 6 vs. ≥ 6 years old) with lower steady state levels found in the younger age group.

Another important issue described in this study is trough level distribution in patients with impaired renal function. Since the therapeutic efficacy of teicoplanin is not inferior to vancomycin with lesser renal toxicity, teicoplanin is preferred in patients with decreased renal function.[28,29] Previous studies were mostly confined to adult population with various settings of renal replacement therapy since the early era of teicoplanin.[30-34] In those studies, adult patients with renal failure tended to have prolonged half-life and reduced total body clearance of teicoplanin, while volume of distribution varied. Lam et al.[35] have suggested a nomogram for dosage adjustment in adults with varying degrees of renal failure. Pharmacokinetics studies of teicoplanin in pediatric patients with impaired renal function have been performed. However, most of them had a focus on the population pharmacokinetics model.[15,16] Moreover, in some pediatric studies, patients with impaired renal function were intentionally excluded.[17,20] Sanchez et al.[18] included only one patient with a moderate alteration in renal function and failed to observe any difference in drug concentration. Our study included eight patients with decreased renal function. Steady state median trough levels were significantly higher in patients with eGFR less than 70 mL/min/BSA.

There are a couple of studies in which teicoplanin was used as a definite therapy for patients with gram-positive bacteremia. Dufort et al.[14] reported that 76.2% (n = 16/21) of their pediatric subjects had gram-positive infection including eight bacteremia cases. However, their focus was on pharmacokinetic issue. They did not mention microbiological or clinical cure in their results. One prospective pediatric study reported teicoplanin treatment in 20 patients with gram-positive bacterial infection (13 *S. epidermidis* bacteremia, two *E. fecium* bacteremia, two methicillin-resistant *S. aureus* [MRSA] bacteremia, three MRSA pneumonia).[36] All patients with gram-positive infection were cured. No relapse was noted in their study. In our study, eight patients had bacteremia due to gram-positive organisms. All

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eight patients were microbiologically cured at day 14 without any mortality. It was concerning that one patient developed breakthrough bacteremia while on teicoplanin therapy. However, two patients with gram-positive bacteremia finished their treatment course with teicoplanin when they developed adverse reaction to vancomycin. Overall, outcomes were favorable in seven of eight patients with bacteremia. Therefore, usefulness of teicoplanin should not be ignored and teicoplanin can be considered as a possible option for gram-positive bacteremia.

Our study has some limitations. First, this was a retrospective study that included only the first steady state levels. Details on dose modification and changes in serial trough levels were not analyzed in all patients. In addition, not all patients had albumin levels measured at the same time when the drug levels were measured. Second, this study did not analyze adverse events or safety in a systematic way. Third, because a small number of patients were enrolled, our observation on the treatment effect of teicoplanin in patients with gram-positive bacteremia needs to be interpreted with caution.

In conclusion, this study provides additive information on the therapeutic drug level monitoring of teicoplanin in children with impaired renal function and some treatment effect in patients with gram-positive bacteremia. Careful monitoring for steady state trough levels of teicoplanin is needed to determine the best dosing regimen to achieve optimal therapeutic levels for infants and young children.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Characteristics and clinical data of patients with toxic trough level

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Supplementary Table 2

Multivariate odds ratios for achievement of target trough level

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Supplementary Fig. 1

Data exclusion flow chart.

Click here to view

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