International Journal of Antimicrobial Agents 46 (2015) 164–168

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Changes in the pharmacokinetics of teicoplanin in patients with hyperglycaemic hypoalbuminaemia: Impact of albumin glycosylation on the binding of teicoplanin to albumin

Tomoyuki Enokiya, Yuichi Muraki, Takuya Iwamoto, Masahiro Okuda *

Department of Pharmacy, Mie University Hospital, Faculty of Medicine, Mie University, 2-174 Edobashi, Tsu 514-8507, Mie, Japan

ARTICLE INFO

Article history:
Received 4 November 2014
Accepted 8 March 2015

Keywords:
Teicoplanin
Hyperglycaemia
Hypoalbuminaemia
Albumin binding
Glycosylated albumin

ABSTRACT

There is large interindividual variability in serum teicoplanin (TEIC) concentrations after administration of a loading dose, and the factors that influence the pharmacokinetics of TEIC are disputed. The aim of this study was to clarify changes in the pharmacokinetics of TEIC that occur in patients with hyperglycaemia as well as the impact of albumin glycosylation on the pharmacokinetics of TEIC. This study consisted of retrospective and prospective investigations. The pharmacokinetic parameters of TEIC were retrospectively compared between patients receiving TEIC treatment. Ninety-four patients were divided into four groups according to their serum albumin and blood glucose concentrations [(i) hyperglycaemic hypoalbuminaemia (albumin < 3.0 g/dL) (n = 16); (ii) non-hyperglycaemic hypoalbuminaemia (n = 29); (iii) hyperglycaemic normoalbuminaemia (albumin ≥ 3.0 g/dL) (n = 9); and (iv) non-hyperglycaemic normoalbuminaemia (n = 40)]. In addition, the concentration of glycosylated albumin was prospectively determined in 28 patients. At 12 h after administration of a loading dose, patients with hyperglycaemic hypoalbuminaemia displayed significantly lower serum TEIC concentrations (P < 0.05) and higher TEIC volume of distribution (V_d) (P < 0.05) than the other three groups, whereas TEIC clearance did not differ significantly among the groups. In addition, the percentage of glycosylated albumin was significantly correlated with the association constant (K_a) of TEIC for albumin (r = 0.53, P = 0.004) and the V_d (r = 0.41, P = 0.031). These results suggest that hyperglycaemic hypoalbuminaemia lowers the serum TEIC concentration, which is attributable to the decreased K_a and increased V_d of TEIC by albumin glycosylation.

1. Introduction

Teicoplanin (TEIC) is an effective treatment for infections caused by Gram-positive bacteria, including meticillin-resistant *Staphylococcus aureus* (MRSA) [1]. According to Harding et al. [2], the mean trough concentration of TEIC is correlated with the clinical outcome of patients with *S. aureus* septicaemia. It has also been reported that administration of inappropriate initial therapies for MRSA infection is associated with higher in-hospital mortality [3,4]. Therefore, when TEIC is used it is important to promptly achieve an effective serum concentration of the drug. However, there is large interindividual variability in serum TEIC concentrations after administration of a loading dose [5,6], and the factors that influence the pharmacokinetics of TEIC have not been fully elucidated.

TEIC binds strongly to serum proteins (mainly albumin), and the free fraction of the drug accounts for 6–12% of its total serum concentration in normal subjects [7]. However, it has been reported that the free fraction of TEIC is increased in patients with serum albumin levels of <3.0 g/dL [8]. Moreover, patients with hypoalbuminaemia were demonstrated to have lower serum trough concentrations of TEIC than healthy volunteers [7]. Thus, it is considered that an increased unbound TEIC fraction results in a greater volume of distribution (V_d) or increased clearance (CL) of the drug, which can lead to a reduced serum concentration of TEIC [7]. In a previous population pharmacokinetic (PPK) study involving Japanese patients with systemic MRSA infections, Ogawa et al. [9] reported that the serum albumin concentration was a significant covariate for the peripheral V_d of TEIC. On the other hand, Nakayama et al. [10] indicated that the serum albumin concentration had no significant influence on the final PPK model. Therefore, the impact of albumin on the pharmacokinetics of TEIC is disputed.

Glycosylation of albumin occurs via a non-enzymatic process involving Schiff base formation and Amadori rearrangement

* Corresponding author. Tel.: +81 59 231 5081; fax: +81 59 232 1201.
E-mail address: okudam@clin.medic.mie-u.ac.jp (M. Okuda).

http://dx.doi.org/10.1016/j.ijantimicag.2015.03.010
0924-8579/

to a ketoamine derivative, and the proportion of albumin that is glycosylated increases with the blood glucose concentration [11,12]. Glycosylation of albumin modifies its physical and biological properties and decreases its ability to bind to albumin-binding drugs (e.g. sulphonylureas, warfarin, phenytoin, valproic acid, nelfinavir, etc.) [13–15]. Furthermore, a rat model of diabetes mellitus was found to exhibit a significantly lower area under the concentration–time curve (AUC) value for nelfinavir than control rats [15]. However, it remains unclear whether binding of TEIC to albumin is affected by glycosylation.

To the best of our knowledge, changes in TEIC pharmacokinetics in patients with hyperglycaemia are yet to be investigated. Such an investigation could help to better describe interindividual variability in TEIC pharmacokinetics. The aim of this study was to clarify the changes in the pharmacokinetics of TEIC that occur in patients with hyperglycaemia as well as the impact of albumin glycosylation on TEIC pharmacokinetics.

2. Materials and methods

2.1. Patients

This study consisted of retrospective and prospective components. The retrospective study included 130 patients and ran from March 2005 to March 2010 at Mie University Hospital (Tsu, Mie, Japan). Patients were enrolled if they fulfilled the following inclusion criteria: (i) their serum TEIC and albumin concentrations were measured on the same day; and (ii) their fasting blood glucose level was measured daily or every other day within a week before administration of TEIC. Patients were excluded if they were ≤15 years old, were receiving renal replacement therapy, had missing data or were using albumin-containing products. The prospective study involved another 41 patients who were administered TEIC and was conducted from April 2010 to October 2010 at Mie University Hospital. Patients were enrolled if their serum TEIC concentration was measured. Exclusion criteria were same as for the retrospective study. Demographic data were obtained by reviewing electronic medical records from the patients with TEIC administration. All patients received an initial loading dose (200 mg or 400 mg every 12 h or every 24 h on Days 1 and 2), and the serum TEIC concentration was determined between Day 3 and Day 7. This study was conducted in accordance with the Declaration of Helsinki and its amendments and was approved by the Ethics Committee of Mie University Graduate School of Medicine and Faculty of Medicine.

2.2. Serum samples

In each study, serum samples were separated from whole blood by centrifugation at 1700 × *g* for 10 min using serum separation tubes, and the total TEIC concentration was determined immediately. The rest of the serum sample was stored at −20 °C until it was used to determine the concentrations of glycosylated albumin and unbound TEIC.

2.3. Assay method

Total serum TEIC concentrations were determined using a fluorescence polarisation immunoassay, the INNOFLUOR® Teicoplanin Assay System (Seradyn, Indianapolis, IL), and the TDx FLx® system (Abbott Laboratories, Chicago, IL). Unbound TEIC was separated by ultrafiltration using a YM-30 Centrifree® device (Nihon Millipore KK, Tokyo, Japan). Certain parameters of the TDx FLx system were changed to allow a lower concentration range to be used during quantification of the serum concentration of unbound TEIC according to a modified version of the method devised by Yano et al. [8]. The accuracy, linearity and precision of this method were evaluated [expressed as the percentage coefficient of variation (%CV)]. Calibration curves were constructed for each TEIC fraction using five samples with concentrations of 0.25, 0.5, 1.0, 2.5 and 5.0 μg/mL. The intraday and interday precision and accuracy of the assay were assessed by analysing nine control samples with concentrations of 0.25, 0.5 and 1.0 μg/mL (n = 3 each) on the same day and examining the mean values obtained for these samples over 5 days. Each sample was prepared by adding TEIC to albumin-free serum. The albumin-free serum was separated from pooled serum by ultrafiltration using a YM-30 Centrifree® device (L-CONSERA I EX; Nissui Pharmaceutical, Tokyo, Japan). The concentration of glycosylated albumin was determined by an enzymatic method using a Lucica® GA-L Kit (Asahi Kasei Pharma Corp., Tokyo, Japan).

2.4. Comparison of teicoplanin pharmacokinetics between patients with and without hypoalbuminaemia and hyperglycaemia

Patients were categorised into two groups based on their serum albumin concentration, i.e. hypoalbuminaemia (albumin < 3.0 g/dL) and normoalbuminaemia (albumin ≥ 3.0 g/dL). The two groups were then further divided into two subgroups based on the patient's blood glucose level, i.e. hyperglycaemic patients and non-hyperglycaemic patients. Hyperglycaemic patients were defined as those who satisfied either of the following inclusion criteria: (i) a fasting blood glucose level of >126 mg/dL persistently during 8 days before TEIC therapy; or (ii) patients who were receiving total parenteral nutrition and exhibited blood glucose levels of >126 mg/dL throughout the day.

For the above four groups, the pharmacokinetic (PK) parameters of TEIC were calculated based on each patient's demographics. The serum trough TEIC concentration at 12 h after administration of the loading dose was also predicted. In addition, the patients' demographic and PK parameters were compared among the four groups.

2.5. Impact on glycosylated albumin on teicoplanin pharmacokinetics

The proportion of glycosylated albumin was obtained by dividing the glycosylated albumin concentration by the albumin concentration for each patient in the prospective study. The relationships between the percentage of glycosylated albumin and each PK parameter [association constant (K_a) of TEIC for albumin, V_d and CL] were analysed. The albumin molecule has been reported to have a single binding site for TEIC [16]. Therefore, the K_a of TEIC for albumin is defined by the following equation:

$$K_a = \frac{b}{f(P-b)}$$

$$b = t - f$$

where b, f and t refer to the molar concentrations of bound, free and total TEIC, respectively, and P is the total molar concentration of albumin. The molecular weights of albumin and TEIC were defined as 67 000 Da and 1700 Da, respectively.

2.6. Pharmacokinetic and statistical analyses

The PK parameters and serum concentrations of TEIC at 12 h after the loading dose were predicted using a Bayesian method by inputting the patients' information (age, sex, weight, serum creatinine and measured serum TEIC concentration) and each dose regimen into the TDM Supporting Software for TEIC v.2.1 (Astellas Pharma, Tokyo, Japan) [10]. Statistical analyses were performed

Table 1
Demographic characteristics of 94 patients in the retrospective study.

Characteristic	Hypoalbuminaemia		Normoalbuminaemia	
	Hyperglycaemic (n = 16)	Non-hyperglycaemic (n = 29)	Hyperglycaemic (n = 9)	Non-hyperglycaemic (n = 40)
Sex (male/female) (n)	11/5	18/11	6/3	15/25
Age (years)	68 (59–77)	64 (19–92)	62 (18–74)	62 (19–81)
Body weight (kg)	56 (37–72)	50 (34–85)	64 (35–80)	50 (33–72)
Serum albumin (g/dL)	2.4* (1.9–2.7)	2.5* (1.8–2.9)	3.2 (3.0–3.7)	3.4 (3.0–4.2)
Serum creatinine (mg/dL)	0.55 (0.34–2.30)	0.61 (0.30–1.90)	0.67 (0.30–0.77)	0.60 (0.35–2.06)
Creatinine clearance (mL/min)[a]	88.7 (26.5–126.8)	66.7 (26.2–263.6)	112.3 (73.8–142.1)	87.0 (20.0–195.2)
Loading dose of TEIC (mg)[b]	1200 (600–1600)	1200 (600–1600)	1200 (600–1600)	800 (400–1600)
Loading dose of TEIC relative to body weight (mg/kg)	18.5 (10.3–33.5)	21.4 (9.4–35.4)	16.3 (10.3–29.1)	17.5 (7.0–36.4)
Measured TEIC concentration (μg/mL)	8.1 (2.4–19.0)	11.3 (3.1–20.9)	10.5 (2.4–17.8)	10.3 (3.8–30.7)

TEIC, teicoplanin. Data are the median (range) unless otherwise stated.
[a] Creatinine clearance was calculated using the Cockcroft–Gault equation.
[b] The loading dose was defined as the total dose administered during the first 2 days of treatment.
* $P < 0.001$ with Bonferroni correction among four groups.

using GraphPad Prism v.4.03 (GraphPad Software Inc., San Diego, CA) and JMP® v.7.0.1 (SAS Institute, Cary, NC). Fisher's exact test and the Mann–Whitney U-test combined with Bonferroni multiple comparisons test were used for comparisons among several groups. Spearman's rank correlation coefficient was used to determine the relationships between the percentage of glycosylated albumin and the K_a of TEIC for albumin, V_d and CL. Significance was established at a P-value of <0.05.

3. Results

3.1. Patients

According to the inclusion and exclusion criteria, 94 of 130 patients were enrolled in the retrospective study. As shown in Table 1, patients were classified into the following four groups: (i) hyperglycaemic hypoalbuminaemia (n = 16); (ii) non-hyperglycaemic hypoalbuminaemia (n = 29); (iii) hyperglycaemic normoalbuminaemia (n = 9); and (iv) non-hyperglycaemic normoalbuminaemia (n = 40). In addition, 28 of 41 patients were enrolled in the prospective study by the exclusion criteria. The patients' demographics, including their PK parameters, are shown in Table 2.

Table 2
Demographic characteristics and pharmacokinetic parameters of 28 patients enrolled in the prospective study.

Characteristic	Median (range)
Sex (male/female) (n)	21/7
Age (years)	63.5 (16–81)
Body weight (kg)	60.0 (40.0–90.0)
Serum albumin (g/dL)	2.9 (2.0–4.9)
Serum creatinine (mg/dL)	0.7 (0.4–4.1)
Creatinine clearance (mL/min)[a]	102.0 (25.3–228.0)
Glycosylated albumin (%)	34.0 (16.0–65.5)
Loading dose of TEIC (mg)[b]	1600 (600–1600)
Loading dose relative to body weight (mg/kg)	26.3 (6.7–38.8)
Total concentration of serum TEIC (μg/mL)	10.9 (2.1–23.6)
Free concentration of serum TEIC (μg/mL)	1.8 (0.5–3.5)
Albumin binding rate of TEIC (%)	83.6 (72.7–92.1)
Association constant of TEIC for albumin ($\times 10^4$/M)	1.3 (0.7–2.1)
CL (L/h)	0.67 (0.35–1.35)
V_d (L)	90.6 (30.0–137.5)
V_d relative to body weight (L/kg)	1.4 (0.5–3.3)

TEIC, teicoplanin; CL, drug clearance; V_d, volume of distribution. Data are the median (range) unless otherwise stated.
[a] Creatinine clearance was calculated using the Cockcroft–Gault equation.
[b] The loading dose was defined as the total dose administered during the first 2 days of treatment.

3.2. Validation of the assay used to assess the unbound fraction of teicoplanin

The correlation coefficient of the calibration curve was 0.997. The accuracy of the assay at TEIC concentrations of 0.5, 1.0 and 2.5 μg/mL ranged from 92% to 112%. In the intraday and inter-day assays, the %CV of the three test samples were <6% and <4%, respectively.

3.3. Comparison of teicoplanin pharmacokinetics between patients with and without hypoalbuminaemia and hyperglycaemia

In the retrospective study, none of the demographic parameters exhibited significant differences among the four groups (Table 1). However, at 12 h after administration of the loading dose, patients with hyperglycaemic hypoalbuminaemia displayed significantly lower serum TEIC concentrations than the other three groups ($P < 0.05$; Fig. 1A). Moreover, this group also demonstrated significantly higher V_d values than the other three groups ($P < 0.05$; Fig. 1B), whereas CL did not differ significantly among the four groups (Fig. 1C).

3.4. Impact of glycosylated albumin on teicoplanin pharmacokinetics

In the prospective study, significant correlations were detected between the percentage of glycosylated albumin and the K_a of TEIC for albumin ($r = 0.53$, $P = 0.0040$; Fig. 2A) or V_d ($r = 0.41$, $P = 0.031$; Fig. 2B). No significant correlation was detected between the percentage of glycosylated albumin and CL ($r = 0.00070$, $P = 0.89$; Fig. 2C).

4. Discussion

To the best of our knowledge, this study is the first demonstration that patients with hyperglycaemic hypoalbuminaemia display lower serum total TEIC concentrations and decreased TEIC association constants for albumin. These findings might help to increase our understanding of interindividual variability in the pharmacokinetics of TEIC.

The findings of the present study suggest that reductions in the TEIC K_a for albumin and increases in V_d are correlated with glycosylation of albumin. It is known that albumin has two main drug binding sites, Sudlow site I and Sudlow site II [17]. The main glycosylation sites of human serum albumin are located in the vicinity of the drug binding sites, and glycosylation of

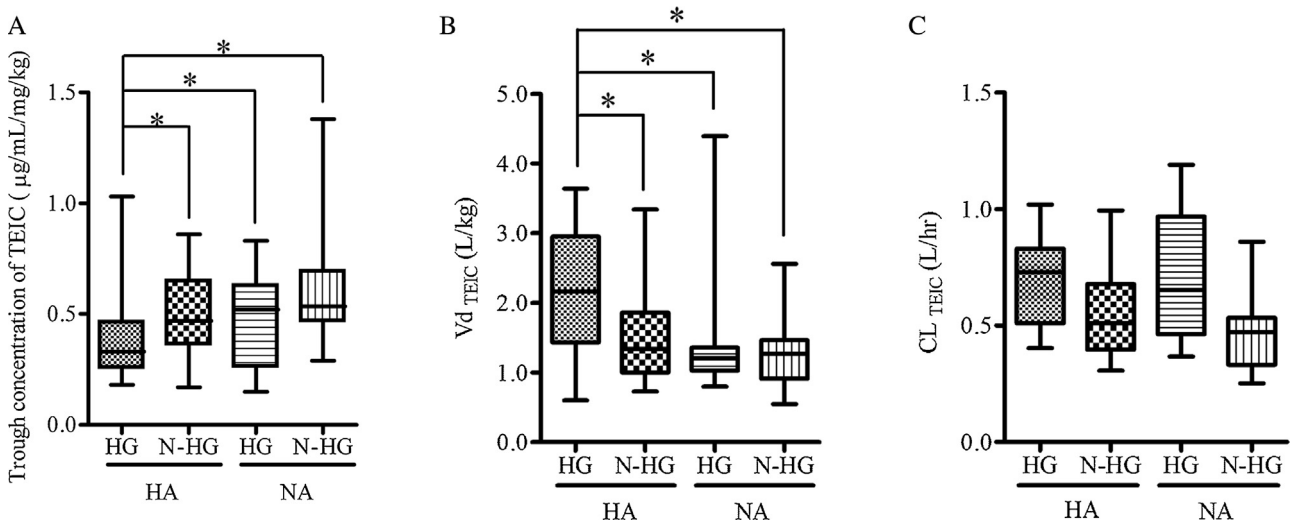

Fig. 1. Comparison between teicoplanin (TEIC) pharmacokinetics in hyperglycaemic and non-hyperglycaemic patients among 94 patients in the retrospective study. HG, hyperglycaemic patients; N-HG, non-hyperglycaemic patients; HA, hypoalbuminaemia; NA, normoalbuminaemia; V_d, volume of distribution; CL, clearance. * $P < 0.05$ (adjusted using Bonferroni correction).

albumin reduces the binding capacity of drug binding sites I (warfarin, phenytoin) and II (valproic acid) [13]. Furthermore, in diabetic rats the AUC of total nelfinavir, which binds strongly to albumin, was significantly decreased following intravenous administration of the drug (control, 1.75 ± 0.08 μg h/mL vs. diabetic, 1.36 ± 0.17 μg h/mL), although the AUC of the unbound fraction was increased. Therefore, the albumin binding rate and the V_d of nelfinavir appear to be changed by glycosylation of albumin [15]. Likewise, the results of the current study can be explained by the hypothesis that the conformational changes in the albumin molecule induced by glycosylation decrease its TEIC binding capacity, resulting in an increase in V_d.

In the prospective study, it was demonstrated that the proportion of glycosylated albumin was positively correlated with V_d, but not CL (Fig. 2). However, most drugs that are mainly excreted in urine display increased renal clearance when the free fraction of the drug is increased [18]. This contradiction might be explained as follows: (i) TEIC distributes highly to the skeletal muscle, pericardium, myocardium and so on [7], although the renal clearance of TEIC is relatively low (renal clearance 12.1 mL/min) [19]. Therefore, we speculated that TEIC clearance might be unaffected by the glycosylation of albumin, even though the free fraction increased. (ii) Hyperglycaemia-induced metabolic and haemodynamic pathways, such as the activation of protein kinase C, acceleration of the polyol pathway, and oxidative stress, cause damage to the kidneys [20]. Indeed, in the present study a negative correlation was detected between creatinine clearance and the proportion of glycosylated albumin, although it was not statistically significant (data not shown; Spearman's rank correlation coefficient = −0.31, $P = 0.11$). On the other hand, a positive correlation was observed between creatinine clearance and CL (data not shown; Spearman's rank correlation coefficient = 0.51, $P < 0.001$). Therefore, it was speculated that the influence of glycosylated albumin on CL might have been offset by the reduction in creatinine clearance caused by hyperglycaemia.

Our finding that the TEIC K_a for albumin is affected by glycosylation might provide useful information not only for determining the optimal dosing regimen for patients with hyperglycaemia but also for identifying factors that influence the pharmacokinetics of TEIC. However, the present study had some limitations that need to be considered. First, clinical outcomes were not evaluated because this study focused on changes in the pharmacokinetics of TEIC induced by a hyperglycaemic state. In addition, it was difficult to exclude the potential effects of other unknown cofounders in the retrospective study.

In the antimicrobial treatment of MRSA infections, it is important to achieve a sufficient serum concentration of the administered drug as early as possible [4]. It was reported that hypoalbuminaemia was an independent risk factor (odds ratio = 0.34) for global mortality from severe sepsis or septic shock [21]. Furthermore, Laupland et al. [22] found that diabetes was an important risk factor (risk ratio = 14.7) for MRSA bacteraemia. In the present

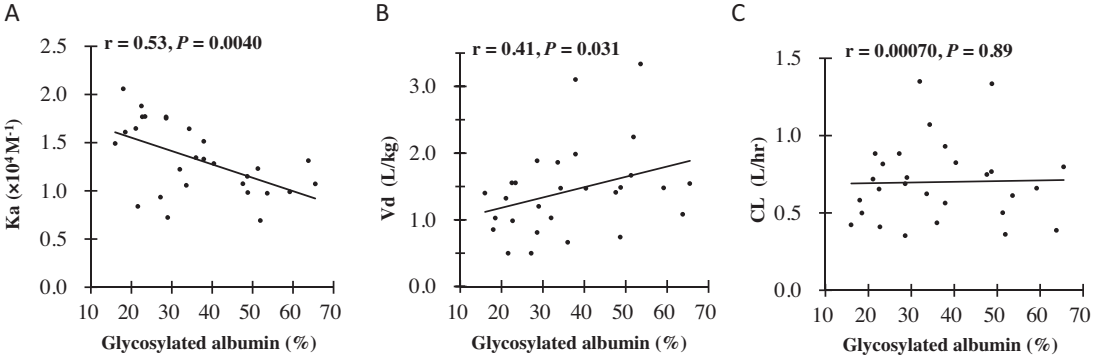

Fig. 2. Correlation between the percentage of glycosylated albumin and (A) the association constant of teicoplanin (TEIC) for albumin (K_a), (B) the volume of distribution (V_d) and (C) clearance in 28 patients in the prospective study.

study, we found that patients with hyperglycaemic hypoalbuminaemia had lower serum TEIC concentrations after a loading dose than patients with non-hyperglycaemic hypoalbuminaemia, hyperglycaemic normoalbuminaemia and non-hyperglycaemic normoalbuminaemia. However, in the hyperglycaemic hypoalbuminaemia patients, the serum trough concentration 12 h after a loading dose exceeded 10 μg/mL when the loading dose was >1600 mg (data not shown). Therefore, TEIC regimens with a high loading dose might be required for patients with hyperglycaemic hypoalbuminaemia to avoid low serum TEIC concentrations.

In conclusion, patients with hyperglycaemic hypoalbuminaemia exhibit lower serum TEIC concentrations following administration of a loading dose. In addition, it was suggested that glycosylated albumin decreases the association constant of TEIC for albumin. A PPK study that includes glycosylation of albumin as a parameter is needed to identify the impact of albumin glycosylation on the pharmacokinetics of TEIC.

Funding

This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science [no. 22926005].

Competing interests

None declared.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and its amendments and was approved by the Ethics Committee of Mie University Graduate School of Medicine and Faculty of Medicine (Tsu, Mie, Japan) [approval no. 1191].

References

[1] Svetitsky S, Leibovici L, Paul M. Comparative efficacy and safety of vancomycin versus teicoplanin: systematic review and meta-analysis. Antimicrob Agents Chemother 2009;53:4069–79.
[2] Harding I, MacGowan AP, White LO, Darley ES, Reed V. Teicoplanin therapy for *Staphylococcus aureus* septicaemia: relationship between pre-dose serum concentrations and outcome. J Antimicrob Chemother 2000;45:835–41.
[3] Khatib R, Saeed S, Sharma M, Riederer K, Fakih MG, Johnson LB. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of *Staphylococcus aureus* bacteremia. Eur J Clin Microbiol Infect Dis 2006;25:181–5.
[4] Schramm GE, Johnson JA, Doherty JA, Micek ST, Kollef MH. Methicillin-resistant *Staphylococcus aureus* sterile-site infection: the importance of appropriate initial antimicrobial treatment. Crit Care Med 2006;34:2069–74.
[5] Pea F, Brollo L, Viale P, Pavan F, Furlanut M. Teicoplanin therapeutic drug monitoring in critically ill patients: a retrospective study emphasizing the importance of a loading dose. J Antimicrob Chemother 2003;51:971–5.
[6] Brink AJ, Richards GA, Cummins RR, Lambson J; Gauteng Understanding Teicoplanin Serum Levels (GUTS) Study Group. Recommendations to achieve rapid therapeutic teicoplanin plasma concentrations in adult hospitalised patients treated for sepsis. Int J Antimicrob Agents 2008;32:455–8.
[7] Wilson AP. Clinical pharmacokinetics of teicoplanin. Clin Pharmacokinet 2000;39:167–83.
[8] Yano R, Nakamura T, Tsukamoto H, Igarashi T, Goto N, Wakiya Y, et al. Variability in teicoplanin protein binding and its prediction using serum albumin concentrations. Ther Drug Monit 2007;29:399–403.
[9] Ogawa R, Kobayashi S, Sasaki Y, Makimura M, Echizen H. Population pharmacokinetic and pharmacodynamic analyses of teicoplanin in Japanese patients with systemic MRSA infection. Int J Clin Pharmacol Ther 2013;51:357–66.
[10] Nakayama K, Gemma H, Kaibara A, Niwa T. Population pharmacokinetics of teicoplanin in adult patients. Jpn J Chemother 2006;54:1–6.
[11] Day JF, Thorpe SR, Baynes JW. Nonenzymatically glucosylated albumin. In vitro preparation and isolation from normal human serum. J Biol Chem 1979;254:595–7.
[12] Dolhofer R, Wieland OH. Increased glycosylation of serum albumin in diabetes mellitus. Diabetes 1980;29:417–22.
[13] Shaklai N, Garlick RL, Bunn HF. Nonenzymatic glycosylation of human serum albumin alters its conformation and function. J Biol Chem 1984;259:3812–7.
[14] Rondeau P, Bourdon E. The glycation of albumin: structural and functional impacts. Biochimie 2011;93:645–58.
[15] Sugioka N, Sato K, Haraya K, Maeda Y, Yasuda K, Fukushima K, et al. Effect of streptozotocin-induced diabetes mellitus on the pharmacokinetics of nelfinavir in rats. Biopharm Drug Dispos 2008;29:469–79.
[16] Assandri A, Bernareggi A. Binding of teicoplanin to human serum albumin. Eur J Clin Pharmacol 1987;33:191–5.
[17] Sudlow G, Birkett DJ, Wade DN. The characterization of two specific drug binding sites on human serum albumin. Mol Pharmacol 1975;11:824–32.
[18] Rowland M, Tozer TN. Clinical pharmacokinetics and pharmacodynamics: concepts and applications. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2010.
[19] Buniva G, Del Favero A, Bernareggi A, Patoia L, Palumbo R. Pharmacokinetics of ^{14}C-teicoplanin in healthy volunteers. J Antimicrob Chemother 1988;21:23–8.
[20] Satirapoj B. Nephropathy in diabetes. Adv Exp Med Biol 2012;771:107–22.
[21] Artero A, Zaragoza R, Camarena JJ, Sancho S, González R, Nogueira JM. Prognostic factors of mortality in patients with community-acquired bloodstream infection with severe sepsis and septic shock. J Crit Care 2010;25:276–81.
[22] Laupland KB, Ross T, Gregson DB. *Staphylococcus aureus* bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000–2006. J Infect Dis 2008;198:336–43.