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

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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

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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

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