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Suitability of 5% glucose solution and Solita®-T No. 3 for infusion of tedizolid phosphate

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Abstract

Tedizolid phosphate is a next-generation oxazolidinone drug with activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp. The injectable form of tedizolid is lyophilized, and while the choice of diluent for infusion, which depends on drug properties and the patient's condition, is crucial for drug stability and patient safety, there are no reports on tedizolid stability in infusion solutions other than physiological saline, which is recommended by the manufacturer. Therefore, we investigated the stability of tedizolid in various infusion solutions, including Solita®-T No. 3 and 5% and 50% glucose solutions in comparison with physiological saline, using high-performance liquid chromatography. Tedizolid was not insolubilized in any of the solutions tested. We observed no significant changes in tedizolid concentration up to 48 h after dilution with physiological saline, 5% glucose, and Solita®-T No. 3 infusion solution; however, a significant decrease in tedizolid concentration was observed after dilution in 50% glucose, with a residual concentration at 48 h after dilution of <20%. Further analysis revealed that this was mainly due to the low pH of the 50% glucose solution. Based on our findings, 5% glucose solution and Solita®-T No. 3 infusion solution are suitable for tedizolid infusion in clinical practice.

Keyword: Tedizolid phosphate; methicillin-resistant *Staphylococcus aureus*; vancomycin-resistant *Enterococcus* spp.

1. Introduction

Nosocomial infections caused by antimicrobial-resistant gram-positive pathogens, such as methicillin-resistant *Staphylococcus aureus*（MRSA）and vancomycin-resistant *Enterococcus* spp., have become a worldwide threat. In Europe and the United States, nosocomial infections caused by healthcare-associated（HA-）MRSA and community-acquired（CA-）MRSA are on the rise, and the number of related deaths is increasing[1, 2]. In Japan, nosocomial and community-acquired infections caused by various multidrug-resistant bacteria have become a significant clinical problem, and MRSA reportedly accounts for many of the new infections caused by drug-resistant bacteria[3]. The isolation rates of HA-MRSA from pneumonia and bacteremia samples and of CA-MRSA from skin and soft tissue infection samples are increasing, and there is concern that the number of MRSA infections will further increase owing to its strong transmission ability[4]. Currently clinically used anti-MRSA drugs include glycopeptide, aminoglycoside, cyclic lipodepsipeptide, and oxazolidinone antibacterial drugs.

Oxazolidinone antibacterials bind to the 50S ribosomal subunit and thus inhibit the formation of the 70S initiation complex, thereby inhibiting bacterial protein synthesis and growth. Recently, tedizolid phosphate（formerly torezolid, trade name Sivextro®）was approved for clinical use, becoming the second agent of this class after linezolid to be available in clinical practice. Tedizolid can be administered via the oral and parenteral routes, e.g., via intravenous drip infusion, and tedizolid administration can be switched from the intravenous to

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oral route without dose modification, even in patients with high drug bioavailability and impaired renal function[5].

The choice of diluent for infusion may be crucial, depending on the patient's condition. The injectable form of tedizolid is lyophilized, and the package insert recommends using physiological saline (isotonic sodium chloride solution) as a diluent[5]. It has been reported that tedizolid is incompatible with any solutions that contain divalent cations, such as calcium chloride, calcium gluconate, and magnesium sulfate, including Ringer's lactate solution and Hartmann's solution[6]. However, there are no reports on whether other infusion solutions, such as 5% glucose, which is widely used as a drug diluent, can be used. In this study, we investigated the stability of tedizolid in physiological saline, Solita®-T No. 3, 5% and 50% glucose solution.

2. Materials and Methods

2.1. Reagents

A standard sample of tedizolid phosphate was purchased from MedChemExpres (Princeton, NJ, USA). *p*-Nitroaniline was purchased from BioVision (Milpitas, CA, USA), and 12 molybdo (IV) phosphoric acid *n*-hydrate (phosphomolybdic acid, PMA) was purchased from Nacalai Tesque (Kyoto, Japan). Tedizolid phosphate for clinical use was purchased from MSD Corp. (Sivextro®, Tokyo, Japan). Dimethyl sulfoxide (DMSO) and acetonitrile were obtained from Wako Pure Chemicals Co. (Osaka, Japan). Thin-layer chromatography (TLC) plates precoated with silica gel (60F-254, 20 cm × 20 cm) were purchased from Merck (Darmstadt, Germany). Physiological saline for injection and 5% and 50% glucose solutions were purchased from Otsuka Pharmaceutical Factory (Tokyo, Japan). Solita®-T No. 3 (a glucose, lactate, and electrolyte-containing infusion solution) was purchased from Yoshindo Inc. (Toyama, Japan). The compositions of all solutions tested in this study are presented in Table 1.

2.2. Methods

Tedizolid diluted in physiological saline, 5% and 50% glucose solutions, and Solita®-T No. 3 was sampled every 0, 1, 12, 24, and 48 hrs, respectively, and the changes in concentration were examined by high-performance liquid chromatography (HPLC). All experiments were conducted under room temperature conditions (25 ± 2°C) with an irradiance of 500 lx.

Table 1 Compositions of the solutions tested in this study (g/250 ml)

Solutions	sodium chloride	poyassium chloride	L-sodium lactate	glucose
Otsuka nomal saline	0.225	-	-	-
Otsuka glucose injection(5%)	-	-	-	12.5
Solita® T No.3	0.225	0.3725	0.56	10.75
Otsuka glucose injection(50%)	-	-	-	125

2.2.1. Preparation of the sample solutions

Tedizolid phosphate was dissolved in distilled water at 50 mg/ml according to the manufacturer's instruction for injection (MSD Corp.) and then diluted with physiological saline, 5% glucose, 50% glucose, or Solita®-T No. 3 infusion solution at 0.8 mg/ml.

2.2.2. Quantitative analysis of tedizolid in dilution

Tedizolid was analyzed by HPLC using a Hibar Lichrosorb RP-18 column (ODS, 5 μm, 4.0 × 120 mm, Kanto Chemical Co., Ltd., Tokyo, Japan). The analytical conditions were set according to previous reports[7,8,9]. In brief, the mobile phase was a mixture of 19.2 mM sodium acetate buffer (pH 7.4) and 15% acetonitrile, the flow rate was 1.0 ml/min, and tedizolid was detected by measuring UV absorbance at 251 nm. The HPLC samples were filtered through a 0.2-μm cellulose acetate filter (AGC Techno Glass, Tokyo, Japan). Diluted

sample solutions of tedizolid（0.45 ml）were collected over time, mixed with 0.5 ml of DMSO containing 0.5 mg *p*-nitroaniline as an internal standard, and then subjected to HPLC analysis. The sample diluted with 50% glucose solution was analyzed using the absolute calibration curve method.

2.2.3. TLC analysis of tedizolid

Tedizolid phosphate in different diluents was partitioned between ethyl acetate and water, and tedizolid was obtained from the ethyl acetate layer. The sample was analyzed by TLC using ethyl acetate as a developing solvent. PMA was used to visualize the analyte, and the analyte complexed with PMA was heated on a plate heater at 150° C for 3 min.

2.2.4. Statistical analysis

Data are expressed as the mean ± SD（n = 4）. Differences between groups were analyzed using Dunnett's test. $P < 0.05$ was considered significant.

3. Results and Discussion

Lyophilized tedizolid phosphate was reconstituted in distilled water（50 mg/ml）and then diluted to 0.8 mg/ml with physiological saline, Solita®-T No. 3, or 5% or 50% glucose solution. The solutions were visually inspected for visible features and turbidity. The tedizolid solutions were colorless or slightly light-yellowish, and no change in appearance was observed during storage at room temperature（25 ± 2° C）for 24 h. To examine the possibility of tedizolid insolubilization by dilution, each dilution was subjected to high-speed centrifugation（10,000 × *g*, 30 min）. No precipitates were observed after centrifugation for any of the solutions. These results suggest that tedizolid is not insolubilized in the solutions tested.

The stability of tedizolid in the various solutions was analyzed using HPLC. Fig. 1 shows the chromatograms of the blank mobile phase and the mobile phase with tedizolid and the internal standard added. In the blank mobile phase, there was no interference peak between tedizolid and the internal standard. The retention time of tedizolid was 3.8 minutes and that of the internal standard was 9.4 minutes. Under the present experimental conditions, the calibration curve showed linearity in the range of 0.125 mg/ml to 1.0 mg/ml, with a regression coefficient of 0.9997. A regression coefficient of 0.99 or higher is generally considered to be evidence that the data fit the regression line well. No significant changes in the concentration of tedizolid were observed up to 48 h after dilution with physiological saline, 5% glucose solution, and Solita®-T No. 3 infusion solution（Fig. 2）. However, a significant decrease in the concentration of tedizolid in the 50% glucose solution was observed, and the residual concentration of tedizolid in this solution at 48 h after dilution was <20%（Fig. 2）. The quantitative HPLC analysis results were supported by TLC findings. The TLC spot of tedizolid did not change for up to 48 h in physiological saline, 5% glucose solution, and Solita®-T

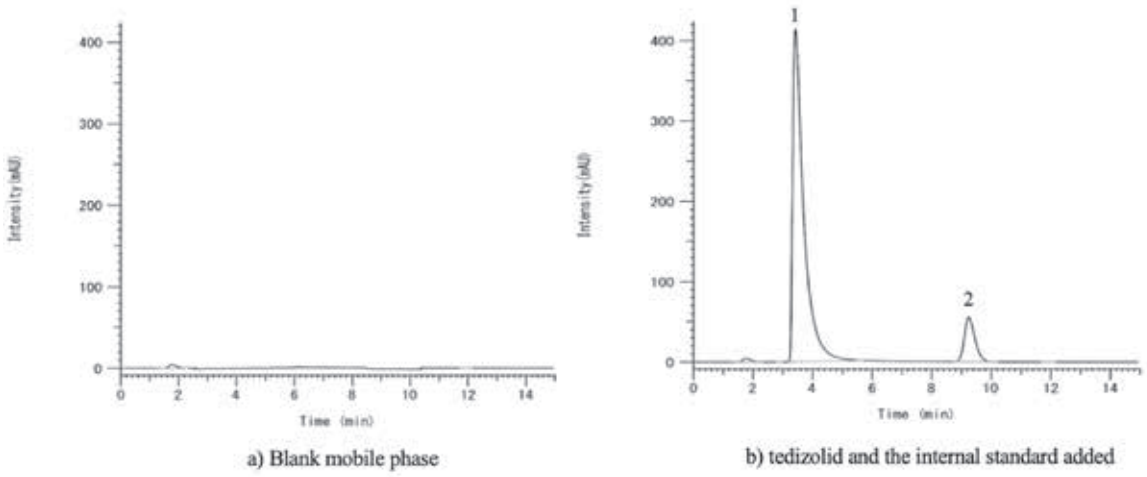

Fig. 1.　HPLC Chromatogram of mobile phase.

1: TZD, 2: I.S: *p*-Nitroanilline 0.1 mg/ml.

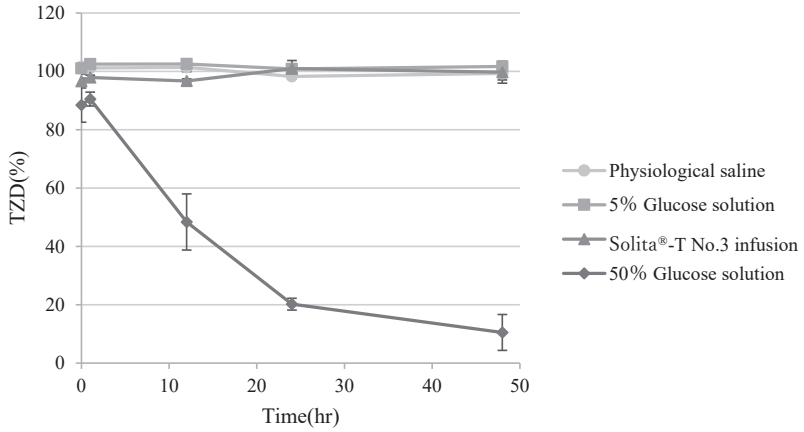

Fig. 2.　Stability of tedizolid in various diluents. Tedizolid diluted with various solutions was sampled for up to 48 h and subjected to HPLC analysis. Data are expressed as the mean ± SD（n = 4）.

No. 3 infusion solution but had nearly disappeared after 48 h in the 50% glucose solution（Fig. 3）. These results suggest that tedizolid is stable in 5% glucose solution and Solita®-T No. 3 infusion solution as well as in saline but not in 50% glucose solution.

The pH of physiological saline, 5% glucose solution, 50% glucose solution, and Solita®-T No. 3 was 7.28 ± 0.09, 7.32 ± 0.06, 2.85 ± 0.04, and 6.71 ± 0.13, respectively. The pH was also checked after one week, but there was no significant change（7.30, 7.25, 2.91,6.60）. To clarify the cause of instability of tedizolid in 50% glucose, the effect of pH on its stability was examined using saline solutions with different pH values prepared by adjusting the pH with hydrochloric acid. After incubation of tedizolid in solutions with different pH values for 48 h, a significant decrease in the tedizolid concentration was observed at low pH（Fig. 4）. These results suggest that the low stability of tedizolid in 50% glucose solution is, at least in part, due to the low pH of the solution. However, the detailed mechanism responsible for the decomposition of tedizolid in 50%

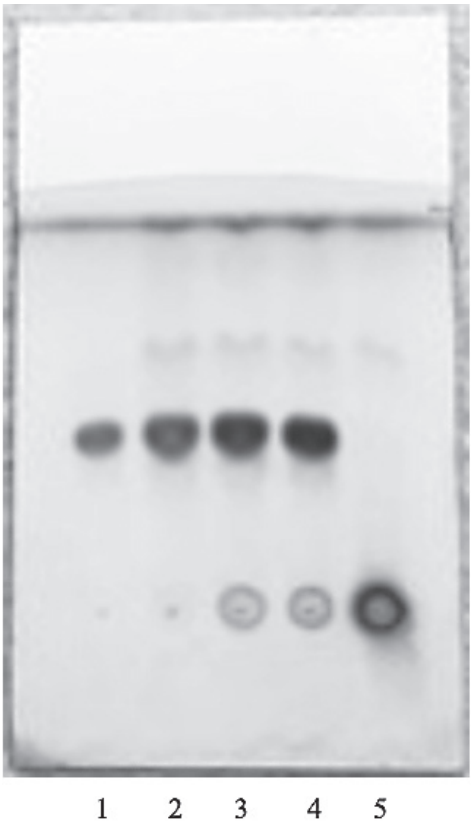

Fig. 3.　TLC Chromatogram of authentic samples.

1: Control, 2: Physiological saline, 3: 5% Glucose solution, 4: Solita®-T No. 3 infusion solution, 5: 50% Glucose solution.

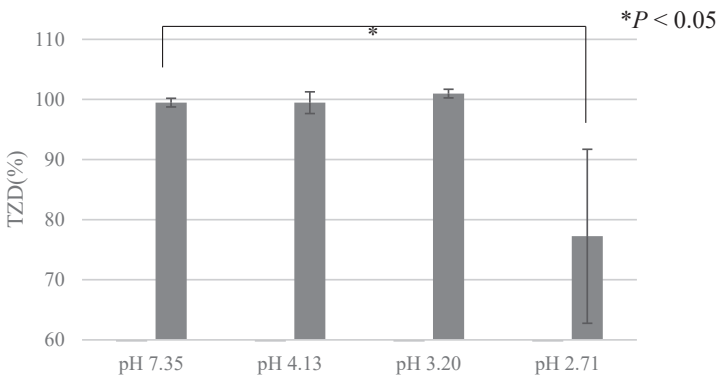

Fig. 4.　Stability of tedizolid in solutions under varying pH conditions. Tedizolid was diluted with saline with varying pH values and immediately subjected to HPLC analysis. Data are expressed as the mean ± SD（n = 4）.

glucose solution remains to be clarified.

Tedizolid was unstable in 50% glucose solution, and the residual rate of tedizolid was ≤ 90% immediately after dilution with 50% glucose（Fig. 2）. Therefore, it is presumed that tedizolid should not be administered from the same line during total parenteral nutrition. The availability of tedizolid administration with a high concentration of glucose via a central vein is of clinical importance but requires further study.

Tedizolid has a high absolute bioavailability and a long half-life. It can be administered intravenously or orally once daily, does not require dose adjustment even in patients with renal dysfunction, and its oral form is stable after crushing[11], making it convenient for clinical use.

The criteria for judging the suitability or incompatibility of injection or infusion solutions are "remain the same in appearance" and "the ingredient is stable for at least 24 h（residual rate of ≥ 90%）"[10]. As neither the 5% glucose solution nor the Solita®-T No. 3 infusion solution showed any change in appearance after tedizolid dilution, and the residual rate at 24 h after dilution was ≥ 90%, it is considered that dilution of tedizolid in 5% glucose solution or Solita®-T No. 3 infusion solution or administration via a side tube are suitable in actual medical practice, as well as dilution with physiological saline. In addition, adsorption to the infusion bag in this experiment was not considered to be a problem because there was no decrease in the concentration of tedizolid diluted in physiological saline.

4. Conclusion

In this study, changes in tedizolid content in various diluents at injection concentrations actually used in clinical practice were evaluated using HPLC. No decrease in concentration over time was observed after dilution with 5% glucose solution and Solita®-T No. 3 infusion or with physiological saline, the dilution solvent recommended in the package insert of tedizolid phosphate. This study identified useful diluents suitable for tedizolid administration in the clinic.

5. Competing interests

There are no conflicts of interest to declare.

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