

Pulmonary Disposition of Tedizolid Following Once-Daily Oral 200 mg Tedizolid Phosphate in Healthy Adult Volunteers

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ABSTRACT

Background: Tedizolid, formerly known as terezolid (TR-700) is a once daily oxazolidinone being investigated for the treatment of pulmonary infections caused by Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus*. This study assessed the pulmonary disposition of TR-700 in healthy adult volunteers after administration of tedizolid phosphate (TR-701).

Methods: Twenty volunteers received 200 mg TR-701 orally q24 h for 3 days to achieve steady state. On day 3, plasma samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h. Protein binding was assessed at 1 h by ultrafiltration. Each subject was randomized to have bronchoalveolar lavage (BAL) samples collected at 2, 6, 12, or 24 h. Drug concentrations in plasma, BAL fluid, and alveolar macrophages (AM) were determined by LC-MS/MS, and the urea correction method was used to calculate epithelial lining fluid (ELF) concentrations. Pharmacokinetic (PK) parameters were estimated by noncompartmental methods and drug penetration was calculated by the ratio of the area under the concentration time curve during the dosing interval (AUC_{0-24}) for ELF and AM to free AUC_{0-24} (AUC_{0-24}) in plasma.

Results: Mean \pm SD half-life, clearance, and volume of distribution in plasma were 9.2 ± 2.0 h, 8.4 ± 2.2 L/h, and 108 ± 21 L, respectively. Total AUC_{0-24} in plasma was 25.1 ± 5.8 $\mu\text{g}\cdot\text{h}/\text{mL}$. Protein binding was $89.4 \pm 1.58\%$, thus resulting in a mean AUC_{0-24} of 2.65 ± 0.72 $\mu\text{g}\cdot\text{h}/\text{mL}$. Mean \pm SD concentrations ($\mu\text{g}/\text{mL}$) in ELF and AM at 2, 6, 12, and 24 h were 0.05 ± 3.83 , 4.45 ± 2.18 , 5.62 ± 1.99 , 1.33 ± 0.50 , and 3.67 ± 1.02 , 4.38 ± 2.18 , 1.42 ± 0.63 , and 1.04 ± 0.52 , respectively. ELF and AM penetration ratios were 41.2 and 20.0.

Conclusions: Plasma PK profile was similar to phase I data previously reported. After administration of TR-701, ELF and AM concentrations of TR-700 exceeded the MIC₉₀ for methicillin-susceptible and -resistant *S. aureus* for the entire dosing interval. This pulmonary profile makes TR-701 a promising agent for further development in respiratory infections.

INTRODUCTION

- Staphylococcus aureus* is a frequently identified pathogen in acute bacterial skin and skin structure infections (ABSSSI), blood stream infections, and lower respiratory tract infections
- MRSA continues to predominate as the most frequent bacterial cause of nosocomial pneumonia¹⁻⁴
- Tedizolid phosphate, formerly known as terezolid phosphate (TR-701) is the prodrug of tedizolid (TR-700), an oxazolidinone active against many common respiratory Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA)

OBJECTIVE

- To define the pulmonary disposition of TR-700 in both the epithelial lining fluid (ELF) and the alveolar macrophages (AM) at steady state in healthy adult participants

MATERIAL and METHODS

Study Design

- Prospective, open-label pharmacokinetic study of the plasma and pulmonary concentrations of TR-700 at steady state
- Subjects were admitted to the Clinical Research Center at Hartford Hospital for one 4 day study period with bronchoscopies and bronchoalveolar lavage (BAL) procedures done at the Same Day Surg-Center at Hartford Hospital

Subjects

- Twenty healthy adult volunteer participants were included in the study
- Inclusion Criteria:** males and females 18 to 55 years of age, body mass index (BMI) between 20 to 34.9 kg/m²; female participants were to be non-pregnant and non-lactating
- Exclusion Criteria:** evidence of clinically significant disease or illness, allergy to TR-701, linezolid or their components, allergy to lidocaine, midazolam, or other anesthetics of similar classes, evidence or history of clinically significant medical abnormalities on physical examination, abnormal laboratory values as outlined in the protocol, history of regular alcohol consumption exceeding 7 drinks/week for females and 14 drinks/week for males, use of tobacco or nicotine-containing products within 6 months prior to admittance to the study center, use of prescription or nonprescription drugs, vitamins, and dietary supplements within 14 days of first dose of study drug with the exception of acetaminophen at doses less than or equal to 1 g/day, the use of any investigational drug within 30 days or 5 half-lives, which ever is longer, and previous enrollment in a TR-701 trial

Study Medication

- TR-701 200 mg tablets were supplied by Trisus Therapeutics, Inc. (San Diego, CA)
- Participants received 200 mg TR-701 with 120 mL water every 24 hours for three days to achieve steady state
- Participants were required to fast from food for 4 hours prior to and 2 hours after study drug administration and 1 hour prior to and after administration with regards to water

Sample Blood Collection

- Blood samples were collected on day 3 at steady state from a peripheral i.v. catheter
- Blood samples were collected at 0 (immediately before drug administration), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after study drug administration for plasma drug concentration determination
- Serum for urea analysis was also collected simultaneously with the bronchoscopy and BAL procedure
- Following centrifugation and separation of plasma within 30 minutes of collection, samples were immediately frozen and stored at -80°C until further analysis

Protein Binding Studies

- Protein binding was assessed in triplicate for each patient at 1 hour post dose administration on day 3
- An aliquot of plasma was centrifuged in a regenerated cellulose 30 kDa molecular weight cutoff ultrafiltration device (Centrifree Centrifugal Filters, Millipore Corporation, Billerica, MA) at 2,000 x g using a fixed angle rotor for 45 minutes at 10°C to obtain ultrafiltrate ($C_{unbound}$); a second aliquot of plasma was retained for total drug concentration determination in the plasma (C_{plasma})
- Protein binding was calculated using the following equation: % protein binding = $100 - (100 \times C_{unbound}/C_{plasma})$

Bronchoscopy and Bronchoalveolar Lavage Procedure

- Participants were randomized to undergo a single bronchoscopy and BAL at 2, 6, 12, or 24 hours (n=5 participants per time point) after the third dose of study drug
- A fiber optic bronchoscope (BF-Q180, Olympus America Inc., Center Valley, PA) was inserted into the medial segment of the right middle lobe of the lung
- Four aliquots of 50 mL 0.9% sodium chloride was instilled and immediately aspirated individually via the bronchoscope
- The first sample of collected BAL fluid was discarded to prevent contamination with larger cell particles and lidocaine, and the remaining three aspirate volumes were recorded and pooled
- Two 4 mL samples were taken from the pooled sample for complete cell count with differential, while the remaining fluid was centrifuged at 400 x g at 4°C for 10 minutes to separate the supernatant and the cell pellet
- The cell pellet was resuspended at a volume equal to 5% of the total pooled BAL volume
- The supernatant and cell pellet were then stored at -80°C until further analysis

Analytical Procedures

- Plasma, BAL fluid supernatant, and BAL fluid cell pellet samples were assayed at Covance, Inc. (Madison, WI), for TR-700 concentrations by validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS)

Urea Concentration Determination

- Urea concentrations in serum and BAL fluid collected simultaneously at the time of bronchoscopy were analyzed by a colorimetric enzymatic assay (Teco Diagnostics, Anaheim, CA) by a spectrophotometer detection method (Cary 50 Series; Varian, Walnut Creek, CA)

Calculation of Drug Concentrations in the ELF and AM

- The volume of ELF within the BAL fluid was calculated by the urea dilution method⁵
- ELF and AM concentrations were calculated by methods previously described by our group^{6,7}
- The number of AM within the BAL fluid was determined from the mean proportion present in the two manual cell counts, and the total volume of these cells in the cell pellet was calculated by using a mean AM volume of $2.42 \mu\text{L}/10^6$ cells

Pharmacokinetic Analyses

- Pharmacokinetics of TR-700 in plasma were estimated for each participant by non-compartmental methods (WinNonlin 5.3, Pharsight Corporation, Mountain View, CA)
- ELF and AM AUC_{0-24} of each pulmonary compartment were calculated using the mean concentrations for the five participants at each time point
- Drug penetration was calculated by the ratio of the AUC_{0-24} for ELF and AM to free AUC_{0-24} (AUC_{0-24}) in plasma

Safety

- Safety and tolerability of TR-701 was monitored by recording adverse events that occurred during the study

RESULTS

Patients

- Of the 20 participants, 17 were male, 15 were Caucasian, 5 were African American, and 4 were of Hispanic ethnicity
- Age ranged from 20 to 50 years with a mean \pm SD of 28 ± 9 years
- Mean \pm SD weight and BMI were 82.4 ± 12.5 kg and 26.7 ± 3.3 kg/m², respectively

Pharmacokinetics

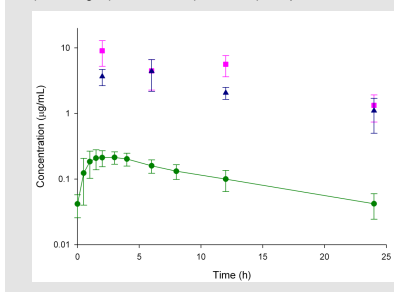
- Plasma pharmacokinetics of TR-700 are listed in Table 1 including results from previously reported Phase I trials
- Protein binding ranged from 86.1% to a maximum of 91.9% with a mean \pm SD $89.4 \pm 1.58\%$
- The free concentration-time profile (Figure 1) resulted in a free area under the concentration-time curve (AUC_{0-24}) of 2.65 ± 0.72 $\mu\text{g}\cdot\text{h}/\text{mL}$

Table 1. Steady-state plasma pharmacokinetics of tedizolid after administration of tedizolid phosphate.

	C_{max} ($\mu\text{g}/\text{mL}$)	C_{min} (range)	AUC_{0-24} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	V_d/F (L)	CL/F (L/h)	$t_{1/2}$ (h)
BAL study (day 3)	2.41 (0.36)	2 (0.5-4)	25.1 (5.8)	108 (21)	8.4 (2.2)	9.2 (2.0)
Bien P (single dose 200 mg orally) (2)	2.0 (0.4)	3 (1-4)	25.4 (4.6)†	128 (31)†	8.1 (1.5)	8.1 (3.6)
Prokocimer P (multiple dose 200 mg orally, day 1) (25)	1.8 (1.2)	3 (1.5-4)	21.6 (6.5)†	155 (29)†	10.0 (2.8)	11.1 (1.2)
Prokocimer P (multiple dose 200 mg orally, steady state) (25)	1.8 (0.4)	3 (2-4)	22.5 (6.5)	143 (51)†	9.5 (2.7)	10.2 (2.0)

Data presented as mean (SD) * V_d/F ; † AUC_{0-24}
 C_{min} = maximum drug concentration; T_{max} = time to C_{max} ; AUC_{0-24} = area under the curve for the dosing interval; V_d/F , Volume of distribution at steady-state; CL/F, total body clearance; $t_{1/2}$, elimination half-life

Figure 1. Tedizolid free plasma (green circles), ELF (pink squares), and AM (blue triangles) concentration (mean \pm SD) time profiles



Pulmonary Pharmacokinetics

- The mean cell counts, % of AM, volume of ELF and volume of aspirated BAL fluid were not statistically different between BAL time points (Table 2)
- Concentrations in both the ELF and AM were greater than that in plasma (Table 3) and greater than the MIC₉₀ for *Staphylococcus* (0.5 $\mu\text{g}/\text{mL}$) and *Streptococcus* (0.25 $\mu\text{g}/\text{mL}$) for the entire dosing interval
- Calculated AUC_{0-24} values for ELF was 109.3 $\mu\text{g}\cdot\text{h}/\text{mL}$ and AUC_{0-24} values for AM was 52.95 $\mu\text{g}\cdot\text{h}/\text{mL}$
- The estimated half life of TR-700 in the ELF and AM based on mean concentrations at each time point were 8.8 and 10.5 hours, respectively
- The penetration ratio into the ELF and AM using the AUC_{0-24} in the respective compartment compared with the AUC_{0-24} in plasma was 41.2 and 20.0, respectively

Table 2. Characteristics of BAL fluid, ELF and AM cell recovery

	BAL Time Point			
	2 h	4 h	12 h	24 h
Cell Count (cells/mL, SD)	3.22E+05 (1.68E+05)	2.29E+05 (8.70E+04)	1.28E+05 (4.23E+04)	2.02E+05 (8.32E+04)
AM (%)	83.5 (13.3)	81.5 (18.9)	83.4 (12.4)	89.0 (6.1)
ELF Volume (mL)	1.65 (0.87)	2.46 (0.86)	1.30 (0.34)	2.53 (1.11)
BAL Volume (mL)	81.8 (12.6)	82.4 (18.3)	101.1 (19.9)	91.4 (17.6)

Data presented as mean (SD)

Table 3. Mean ELF, AM, and plasma concentrations at each BAL time point

	BAL Time Point			
	2 h	4 h	12 h	24 h
ELF ($\mu\text{g}/\text{mL}$)	9.05 (3.83)	4.45 (2.18)	5.62 (1.99)	1.33 (0.59)
AM ($\mu\text{g}/\text{mL}$)	3.67 (1.02)	4.38 (2.18)	1.42 (0.63)	1.04 (0.52)
Total Plasma ($\mu\text{g}/\text{mL}$)	2.01 (0.55)	1.51 (0.33)	0.946 (0.31)	0.398 (0.17)
Free Plasma ($\mu\text{g}/\text{mL}$)	0.213 (0.058)	0.159 (0.035)	0.100 (0.033)	0.042 (0.018)

Data presented as mean (SD)

Safety

- The most commonly reported adverse events were mild and included headache (n=1), nausea (n=1), and bradycardia (n=2).

CONCLUSION

- Steady-state plasma pharmacokinetics in this study were similar to previous studies done in healthy participants
- ELF and AM concentrations were higher than free plasma concentrations over the entire dosing interval
- These data support further clinical investigation of TR-701 for the treatment of pulmonary infections caused by susceptible Gram-positive organisms including MRSA

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