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Pharmacokinetics of Tedizolid in Obese and Nonobese Subjects

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Obesity, defined as body mass index (BMI) ≥ 30 kg/m^2, is a growing problem worldwide; the prevalence is 38% in the US adult population.[1] Obesity is a risk factor for infection and is associated with antimicrobial treatment failure[2] and worse clinical outcomes.[3] Community-acquired pneumonia and skin and soft-tissue infections are the most common indications for prescribing outpatient antibiotics for obese patients.[4] Obesity can affect the ability of antimicrobial agents to attain therapeutic levels.[5,6] Changes in clearance and volume of distribution that may occur in obese patients can alter the dose–exposure relationship with some drugs, resulting in the need to adjust the dose in this patient population.[7] With the emergence of antibiotic resistance, dosing decisions become increasingly important.

Tedizolid phosphate, the prodrug of the novel oxazolidinone tedizolid, has been approved for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) in a number of countries, among them the United States and countries in the European Union.[8,9] Tedizolid phosphate is rapidly and extensively converted by endogenous phosphatases to its microbiologically active moiety, tedizolid, after administration.[10,11] Tedizolid is generally at least 4-fold more potent in vitro than linezolid, the only other currently marketed oxazolidinone antibacterial, against staphylococci (including methicillin-resistant *Staphylococcus aureus*), streptococci, and enterococci (including vancomycin-resistant strains).[10,12,13] In 2 recent phase 3 trials in patients with ABSSSIs, tedizolid (200 mg once daily for 6 days) demonstrated noninferior efficacy to linezolid (600 mg twice daily for 10 days) and was generally well tolerated.[14,15] The pharmacokinetics (PK) of tedizolid allow for once-daily administration, either orally or intravenously, at equivalent doses.[11]

Available data suggest that systemic exposure to linezolid is lower in obese than in nonobese patients, which suggests that body weight and/or BMI may be important factors.[16–18] The reason for this difference remains undetermined, as does whether linezolid dose modification is warranted for obese patients. In studies of tedizolid, exposure in elderly adults, adolescents, and subjects with severe hepatic or renal impairment (including those requiring hemodialysis) was similar to that in control groups following administration of oral or intravenous tedizolid 200 mg.[19,20]

The PK in obese subjects were not explicitly studied during the development of tedizolid, but approximately 28% of subjects in phase 1 studies were obese. Thus, a retrospective comparison of the extensive PK data obtained in obese and nonobese subjects would provide useful knowledge of tedizolid PK in obese patients, which could assist in dosing; this is the basis for the current investigation.

Methods

Ethics

Studies were conducted in accordance with the principles of Good Clinical Practice and were approved by the appropriate institutional review boards and regulatory agencies. The Covance Clinical Research Unit institutional review board approved the protocols, amendments, and informed consent documents before study initiation. Written informed consent was

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Table 1. Studies Providing Source Data for the Noncompartmental PK Analyses

Study	Study Design and Population	Treatment	ClinicalTrials.gov Registration Number
Phase 1[11]	Single ascending dose, multiple dose, absolute bioavailability, and venous tolerability in healthy subjects	Single ascending doses of 100, 200, 300, 400 mg tedizolid phosphate IV; multiple doses of tedizolid 200 mg IV and PO × 7 days (absolute bioavailability, tedizolid 200 mg IV and PO; venous tolerability, tedizolid 200 mg phosphate IV × 3 days)	NCT00983255
Phase 1[20]	Single dose or 2 doses in subjects with advanced renal disease (dialysis and nondialysis) and healthy controls	One or 2 doses of tedizolid phosphate 200 mg IV	NCT01452828
Phase 1[20]	Single PO dose in subjects with moderate or severe hepatic impairment and in healthy controls	Tedizolid phosphate 200 mg PO	NCT01431833
Phase 1[21]	Single PO dose in healthy young (18- to 45-year-old) and healthy elderly (≥65-year-old) subjects	Tedizolid phosphate 200 mg PO	NCT01496677

IV, intravenously; PO, orally.

obtained from all subjects before they underwent any study-related procedures.

Analysis Population

The analysis population consisted of subjects who participated in phase 1 clinical studies and received single oral or intravenous doses of tedizolid. One study examined tedizolid exposure in healthy subjects as part of first in-human dosing, and 3 others examined tedizolid in elderly adults or in subjects with severe hepatic or renal impairment, alongside comparative control groups. Details of the studies (ClinicalTrials.gov registration numbers NCT00983255, NCT01452828, NCT01431833, and NCT01496677) are shown in Table 1.[11,20,21]

Phase 1 subjects were eligible for enrollment if they were in good health based on medical history, physical examination, 12-lead electrocardiogram, vital signs, and laboratory test results, if they tested negative for drugs of abuse, and if they were not pregnant.

Pharmacokinetic Sampling

Full-profile sampling, with collection of blood samples over a 72-hour period, was performed in all phase 1 studies after administration of a single oral or intravenous dose of tedizolid phosphate to each subject. Blood samples were collected before dosing (0 hours) and 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, 48, and 72 hours after dosing. Plasma concentrations of tedizolid were measured using high-performance liquid chromatography–tandem mass spectrometry. Samples were extracted with acetonitrile and precipitated with hydrochloric acid, followed by low-speed (3800 *g*) centrifugation at room temperature for 5 minutes. Supernatants were evaporated to dryness and reconstituted in methanol/water (3:7, vol/vol). Tedizolid and tedizolid phosphate were separated by high-power liquid chromatography (1200 series; Agilent Technologies, Santa Clara, California) with a Hypersil GOLD aQ column (50 × 3 mm, 5-μm particle size; Thermo Fisher Scientific, Waltham, Massachusetts). Samples were eluted using a gradient from 80% 20 mM ammonium phosphate (pH 9.0)/20% methanol to 80% methanol over 4.5 minutes at a flow rate of 0.5 mL/min. The column eluent was directed to an API 4000 triple quadrupole mass spectrometer (AB SCIEX, Framingham, Massachusetts) for compound quantification. Data were processed using the Analyst 1.4.1 software package (AB SCIEX) and the Watson LIMS laboratory information management system (Thermo Fisher Scientific). The lower limit of quantification of tedizolid was 5 ng/mL. A plasma tedizolid concentration below the lower limit of quantification was treated as missing.

Noncompartmental Analysis

Noncompartmental analysis used data from 174 participants in the phase 1 studies to compare the PK of the obese and nonobese groups (obese, n = 38; nonobese, n = 136). Obesity was defined as BMI ≥ 30 kg/m^2, and nonobesity was defined as BMI < 30 kg/m^2. Geometric mean ratios (GMRs) of the observed tedizolid plasma single-dose PK exposure parameters were calculated after single-dose oral or intravenous administration of tedizolid, along with associated 90% confidence intervals (CIs). The PK parameters of interest were maximum plasma concentration (C_{max}) and area under the plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$). Nonobese subjects served as the reference population. The geometric means for C_{max} and $AUC_{0-\infty}$ and the GMRs for obese to nonobese were calculated. Given that the PK/pharmacodynamic target attainment of tedizolid is relatively insensitive to decreases of around one-third in the *f*AUC/minimal inhibitory concentration

Table 2. Observed Plasma Tedizolid Exposure Measures for Obese and Nonobese Healthy Subjects Who Received Oral or Intravenous Tedizolid Phosphate in Phase 1 Clinical Trials GMR

						GMR 90%CI Limits	
Parameter	Route	Weight Classification	n	GM	GMR[a]	Lower	Upper
C_{max}[b]	Oral	Obese	31	1.9	0.82	0.75	0.89
		Nonobese	91	2.3			
	Intravenous	Obese	7	2.5	0.88	0.72	1.07
		Nonobese	60	2.9			
$AUC_{0-\infty}$[c]	Oral	Obese	31	25.4	0.89	0.80	0.99
		Nonobese	86	28.5			
	Intravenous	Obese	7	25.4	0.88	0.73	1.07
		Nonobese	59	28.7			

$AUC_{0-\infty}$, area under the plasma concentration–time curve from zero to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GM, geometric mean; GMR, geometric mean ratio.
[a]GMR is (GM obese)/(GM nonobese).
[b]C_{max} units are μg/mL.
[c]$AUC_{0-\infty}$ units are μg·h/mL.

(MIC) ratio (free-drug area under the concentration–time curve over 24 hours at steady state following a 200-mg dose divided by the MIC of 0.5 μg/mL)[19] and that up to twice the dose was well tolerated in a phase 2 study,[22] the PK in obese and nonobese subjects were considered similar if the GMRs and 90%CIs fell between 0.7 and 1.43.

Results

Noncompartmental Analysis

The $AUC_{0-\infty}$ and C_{max} GMRs and 90%CIs for both intravenous and oral tedizolid phosphate for obese and nonobese healthy subjects were within the prespecified range of 0.7 to 1.43 (Table 2). For both intravenous and oral administration of tedizolid phosphate, $AUC_{0-\infty}$ and C_{max} GMR values were 11% to 18% lower in obese subjects than in nonobese subjects, indicating no clinically meaningful difference in tedizolid exposure measures between the 2 groups. Although C_{max} GMRs and 90%CIs were slightly lower after oral administration than after intravenous administration, the route of administration of tedizolid did not affect plasma exposure, as measured by $AUC_{0-\infty}$, in obese subjects.

Discussion

Alterations of PK parameters in obesity can affect antimicrobial exposure and result in treatment failure. In the noncompartmental analysis reported here, there were no clinically meaningful differences in exposure parameters after intravenous or oral administration of a single 200-mg dose of tedizolid phosphate between obese and nonobese subjects.

In patients with ABSSSIs who received a standard tedizolid regimen of tedizolid phosphate 200 mg once daily, both C_{max} and area under the curve at steady state from 0 to 24 hours ($AUC_{ss(0–24)}$) were unaffected by BMI and total body weight. Although a relationship between tedizolid exposure and ideal body weight (itself a surrogate for lean body weight[23]) or, similarly, between exposure and lean body weight was seen in the univariate analysis, the overall effect has been shown to be not clinically meaningful (based on the ratios of the model-estimated AUC_{ss} extreme values and the corresponding reference AUC_{ss}, which was close to 1).[19]

Given that the PK parameter of importance for the clinical activity of tedizolid is the *f*AUC/MIC ratio,[24] these data showing that the AUC of tedizolid is unaltered in obesity indicate that the 200-mg dose can be used to treat obese patients. These findings are supported by the results of a previously developed population PK model that was used to predict PK exposure from 647 patients with ABSSSIs who participated in phase 3 studies (obese, 193; nonobese, 454). Steady-state tedizolid exposure measures predicted by the population PK model were similar for obese and nonobese patients (data on file). Exposure to tedizolid in these studies was similar in nonobese, obese, and severely obese patients. Median $AUC_{ss(0–24)}$ values of 21.8, 23.3, and 22.3 μg·h/mL in the nonobese, obese, and severely obese groups, respectively, and the overall range of individual exposures were also similar (Figure 1; data on file). Further evidence is provided by a recently published study demonstrating that the PK exposure was similar (~20% lower) in morbidly obese (BMI $\geq$ 40 kg/m^2) and in nonobese subjects, although it should be noted that this was a small-scale study with just 9 subjects per group.[25]

In the 2 phase 3 studies of tedizolid in patients with ABSSSIs, the early clinical response at 48 to 72 hours declined with increasing BMI in tedizolid-treated patients.[26] However, by the posttherapy evaluation,

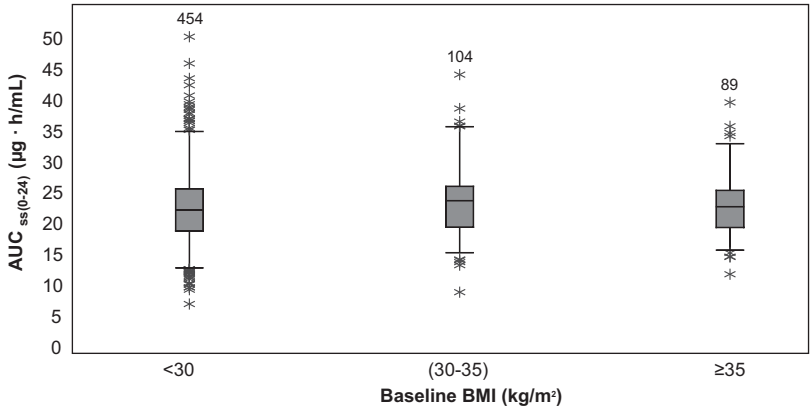

Figure 1. Population PK: tedizolid exposure in nonobese, obese, and severely obese patients. Boxes represent the 25th, 50th, and 75th percentiles, with whiskers extending to the 5th and 95th percentiles. Asterisks show data points outside this range. The number of patients is above each box. $AUC_{ss(0–24)}$, area under the curve at steady state for 0 to 24 hours; BMI, body mass index; PK, pharmacokinetics.

investigator-assessed clinical success rates were similar for patients with BMI < 30 and ≥ 30 kg/m^2 (94.6% and 91.1%, respectively) and were slightly lower for the group with BMI ≥ 35 kg/m^2 (86.0%; data on file). Although no PK differences were found that would be expected to explain the observed treatment differences, other factors in obese patients, including comorbid conditions and differences in distribution to infected tissue, may compromise the response to antibiotics and influence treatment outcomes.

Some evidence from small studies and case reports of patients with varying degrees of obesity suggests that exposure to linezolid is lower in obese patients. Population PK models have suggested a potential relationship between linezolid clearance and body size (ideal body weight[27] and total body weight[28]). At present, there are no dose-adjustment recommendations for linezolid for obese patients.

Conclusions

Obese patients are considered a challenging population to treat. Appropriate dosing of antibiotics in obese patients is difficult and may result in underdosing. Our study shows that at the approved tedizolid phosphate dose of 200 mg once daily, no clinically meaningful differences in exposure to tedizolid were observed between obese and nonobese subjects. These findings suggest that tedizolid may be administered to obese patients without dose adjustment.

Declaration of Conflicting Interests

Philippe Prokocimer and Shawn Flanagan were employees of Merck & Co., Inc., Kenilworth, New Jersey, at the time of the study. Sonia L. Minassian has no financial conflicts of interest to disclose. Julie A. Passarell and Jill Fiedler-Kelly received consulting fees from Cognigen Corporation at the time of the study.

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References

1. American Heart Association. Heart Disease and Stroke Statistics—2017 Update. http://circ.ahajournals.org/content/early/2017/01/25/CIR.0000000000000485.full/pdf. Accessed April 28, 2017.
2. Longo C, Bartlett G, Macgibbon B, et al. The effect of obesity on antibiotic treatment failure: a historical cohort study. *Pharmacoepidemiol Drug Saf*. 2013;22:970–976.
3. Falagas ME, Athanasoulia AP, Peppas G, Karageorgopoulos DE. Effect of body mass index on the outcome of infections: a systematic review. *Obes Rev*. 2009;10:280–289.
4. Counerweight Project Team. The impact of obesity on drug prescribing in primary care. *Br J Gen Pract*. 2005;55:743–749.
5. Janson B, Thursky K. Dosing of antibiotics in obesity. *Curr Opin Infect Dis*. 2012;25:634–649.
6. Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. *Ann Pharmacother*. 2000;34:1066–1069.
7. Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet*. 2010;49:71–87.
8. Sivextro (tedizolid phosphate) [summary of product characteristics]. Hoddesdon, Hertfordshire, UK: Merck Sharp & Dohme Ltd.; 2016.
9. Sivextro (tedizolid phosphate) [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme Corp.; 2016.
10. Schaadt R, Sweeney D, Shinabarger D, Zurenko G. In vitro activity of TR-700, the active ingredient of the antibacterial prodrug TR-701, a novel oxazolidinone antibacterial agent. *Antimicrob Agents Chemother*. 2009;53:3236–3239.
11. Flanagan S, Fang E, Munoz KA, Minassian SL, Prokocimer PG. Single- and multiple-dose pharmacokinetics and absolute bioavailability of tedizolid. *Pharmacotherapy*. 2014;34:891–900.
12. Brown SD, Traczewski MM. Comparative in vitro antimicrobial activities of torezolid (TR-700), the active moiety of a new

oxazolidinone, torezolid phosphate (TR-701), determination of tentative disk diffusion interpretive criteria, and quality control ranges. *Antimicrob Agents Chemother*. 2010;54:2063–2069.
13. Thomson KS, Goering RV. Activity of tedizolid (TR-700) against well-characterized methicillin-resistant *Staphylococcus aureus* strains of diverse epidemiological origins. *Antimicrob Agents Chemother*. 2013;57:2892–2895.
14. Moran GJ, Fang E, Corey GR, Das AF, De Anda C, Prokocimer P. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis*. 2014;14:696–705.
15. Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. *JAMA*. 2013;309:559–569.
16. Muzevich KM, Lee KB. Subtherapeutic linezolid concentrations in a patient with morbid obesity and methicillin-resistant *Staphylococcus aureus* pneumonia: case report and review of the literature. *Ann Pharmacother*. 2013;47:e25.
17. Stein GE, Schooley SL, Peloquin CA, et al. Pharmacokinetics and pharmacodynamics of linezolid in obese patients with cellulitis. *Ann Pharmacother*. 2005;39:427–432.
18. Hamilton R, Thai XC, Ameri D, Pai MP. Oral bioavailability of linezolid before and after Roux-en-Y gastric bypass surgery: is dose modification necessary in obese subjects? *J Antimicrob Chemother*. 2013;68:666–673.
19. Flanagan S, Passarell J, Lu Q, Fiedler-Kelly J, Ludwig E, Prokocimer P. Tedizolid population pharmacokinetics, exposure response, and target attainment. *Antimicrob Agents Chemother*. 2014;58:6462–6470.
20. Flanagan S, Minassian SL, Morris D, et al. Pharmacokinetics of tedizolid in subjects with renal or hepatic impairment. *Antimicrob Agents Chemother*. 2014;58:6471–6476.
21. Dreskin H, Munoz KA, Fang E, et al. Safety and pharmacokinetics of single oral administration of tedizolid phosphate in healthy elderly subjects and adult control subjects. Presented at: Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 52nd Annual Meeting; September 9–12, 2012; San Francisco, CA. Abstract A-1293.
22. Prokocimer P, Bien P, Deanda C, Pillar CM, Bartizal K. In vitro activity and microbiological efficacy of tedizolid (TR-700) against Gram-positive clinical isolates from a phase 2 study of oral tedizolid phosphate (TR-701) in patients with complicated skin and skin structure infections. *Antimicrob Agents Chemother*. 2012;56:4608–4613.
23. Pai MP, Bearden DT. Antimicrobial dosing considerations in obese adult patients. *Pharmacotherapy*. 2007;27:1081–1091.
24. Louie A, Liu W, Kulawy R, Drusano GL. In vivo pharmacodynamics of torezolid phosphate (TR-701), a new oxazolidinone antibiotic, against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* strains in a mouse thigh infection model. *Antimicrob Agents Chemother*. 2011;55:3453–3460.
25. Pai MP. Pharmacokinetics of tedizolid in morbidly obese and covariate matched non-obese adults. *Antimicrob Agents Chemother*. 2016;60:4585–4589.
26. Cubist Pharmaceuticals. Anti-Infective Drugs Advisory Committee Meeting. Tedizolid phosphate for the treatment of acute bacterial skin and skin structure infections; March 31, 2014. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM390790.pdf:1-137. Accessed November 10, 2016.
27. Meagher AK, Forrest A, Rayner CR, Birmingham MC, Schentag JJ. Population pharmacokinetics of linezolid in patients treated in a compassionate-use program. *Antimicrob Agents Chemother*. 2003;47:548–553.
28. Abe S, Chiba K, Cirincione B, Grasela TH, Ito K, Suwa T. Population pharmacokinetic analysis of linezolid in patients with infectious disease: application to lower body weight and elderly patients. *J Clin Pharmacol*. 2009;49:1071–1078.