Pharmacokinetics of Tedizolid in Morbidly Obese and Covariate Matched Non-Obese Adults

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Running Head: Tedizolid Pharmacokinetics in Obesity

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Abstract:
Tedizolid is a novel oxazolidinone antimicrobial administered in its prodrug form, tedizolid phosphate as a fixed once-daily dose. The pharmacokinetics of tedizolid has been studied in relatively small proportion of morbidly obese (BMI ≥ 40 kg/m^2) adults through population analyses with sparse sampling. The current study compared the intensively sampled plasma pharmacokinetics of tedizolid phosphate and tedizolid in 9 morbidly obese to 9 age-, sex-, and ideal body weight-matched non-obese (BMI 18.5 – 29.9 kg/m^2) healthy adult (18-50 years of age) volunteers after administration of a single-intravenous dose of tedizolid phosphate. The median (range) weight was 72.6 (58.9-89.5) kg and 117 (102-176) kg in mostly female (77.8 %) non-obese and morbidly obese adults, respectively. Tedizolid phosphate concentrations were below the limit of quantitation in a majority of subjects after the 2-hour time point. The tedizolid plasma median (range) C_{max} and AUC_{0-inf} was 2.38 (1.28-3.99) mg/L and 26.3 (18.4-43.2) h•mg/L, respectively, in morbidly obese subjects that was non-significantly (p≥0.214) different than values in non-obese subjects. Similarly, the volume of distribution (Vz, p=0.110) and clearance (CL, p=0.214) were comparable between groups. A nearly identical (p=0.953) median tedizolid half-life of approximately 12 hours was observed in both groups. Tedizolid Vz and CL scaled with body weight but not proportionately. The small and non-significant differences in tedizolid AUC_{0-inf} between morbidly obese and non-obese subjects suggest that dose modification is not necessary in morbidly obese adults.
More than one-third of the US adult population is classified as obese based on having a body mass index (BMI) $\geq 30 \text{ kg/m}^2$ (1). Acute bacterial skin and skin structure infections (ABSSSI) are common in obese patients who are predisposed to developing type 2 diabetes (2). Tedizolid is a novel once-daily oxazolidinone that was recently approved for the treatment of ABSSSI at 200 mg daily for 6 days. Tedizolid is a more potent oxazolidinone compared to linezolid and does not interact with selective serotonin reuptake inhibitors (SSRIs). This pharmacological difference is significant because use of antidepressants is higher in obese adults compared to non-obese adults in the United States (3, 4). As a consequence, tedizolid may be selected over linezolid for the treatment of ABSSSI in obese patients that are potentially managed with SSRIs.

To date, population pharmacokinetic (POP-PK) analyses have demonstrated that the concentration-time profile of tedizolid is similar in subjects with class II obesity (BMI $\geq 35$ kg/m$^2$) compared to non-obese adults (BMI $< 30$ kg/m$^2$), suggesting that no dose modification for body size is necessary (5). In addition, POP-PK analyses have clearly demonstrated that the tedizolid volume of distribution and clearance scale as a power term function of ideal body weight (IBW) but not with body weight or BMI (6). This POP-PK analysis suggests that identical doses of tedizolid can be administered in obese and non-obese adult patients of similar stature (6). However, the POP-PK model likely included a relatively small proportion of morbidly obese (BMI $\geq 40$ kg/m$^2$) adults as only one of two Phase 3 trials enrolled patients (27 of 664 subjects) in this body size stratum (5-7).

Two Phase 3 studies, TR701-112 and TR701-113, evaluated the efficacy, safety, and POP-PK of tedizolid 200 mg once daily for 6 days compared to linezolid 600 mg twice daily for 10 days (7). The primary efficacy outcome was early clinical response, defined as $\geq 20\%$
reduction in lesion size, and apyrexia at 48 to 72 hours. In TR701-112, patients with a BMI 35-40 kg/m² had a lower clinical response rate with tedizolid as compared to linezolid (77.9% vs 86.7%). Patients in the tedizolid group with a BMI > 40, who were only recruited in the TR701-113 trial, had an even lower clinical response rate compared to linezolid (59.3% vs 80.8%) (7).

The 95% confidence interval for the response rate difference between these groups crossed zero (not significant) but a trend in the size of the difference is notable across body size (7). A subgroup analysis of the primary endpoint by medical history in the pooled studies showed that patients with diabetes on tedizolid also had a numerically lower response rate compared to patients on linezolid. Although the studies found tedizolid to be non-inferior to linezolid for the primary efficacy outcome, the numerical differences in the diabetic and obese populations cannot be ignored (7). The results of the analyses, albeit insufficiently powered, suggest the potential for different outcomes in obese patients, especially among those with diabetes.

The results of these sub-group analyses prompt a closer examination of the tedizolid dosing schedule in obese adults. The tedizolid AUC and C_{max} is similar after single and multiple doses of intravenous tedizolid that supports the role of a single-dose PK study to characterize the concentration-time profile of this agent (8). If the tedizolid pharmacokinetic parameters are correlated to ideal body weight as suggested by POP-PK analyses, then similar exposures should be expected in morbidly obese and non-obese adults with the same dosage. Thus, the current study was designed to compare the single dose (200 mg) plasma pharmacokinetics of intravenous tedizolid in morbidly obese (≥ 40 kg/m²) to age-, sex-, and ideal body weight-matched non-obese adult volunteers (18.5-29.9 kg/m²). The correlation of tedizolid pharmacokinetic system parameters to body size parameters was also examined.
MATERIALS AND METHODS

Regulatory Review. The current study met the requirement for a waiver of Investigation New Drug application (IND Exempt # 125012). The study was approved by the Albany College of Pharmacy and Health Sciences Institutional Review Board (IRB) and through IntegReview (Austin, TX). This clinical trial was performed at the clinical research unit of TKL Research (Rochelle Park, NJ) and was registered through clinicaltrials.gov; the registry number is NCT02342418.

Inclusion Criteria. Subjects fulfilling the following criteria were eligible: 1.) Males and females, 18 to 50 years of age; 2.) Non-smoking or light-smoking (≤ 5 cigarettes per day) volunteers; 3.) Estimated creatinine clearance (Cockcroft-Gault equation (9)) ≥ 90 mL/min; 4.) Female subjects of childbearing potential either surgically sterilized, using hormonal contraceptives or an effective barrier method of contraception (diaphragm, cervical cap, condom) or agree to abstain from sex from the time of pre-study screening, during the entire study period and 4 weeks following the study period; 5.) Platelets count ≥ 140,000/μL; 6.) Absolute neutrophil count ≥ 1800/μL.

Exclusion Criteria. Subjects fulfilling the following criteria were excluded: 1.) History of hypersensitivity reaction to any oxazolidinone; 2.) BMI < 18.5 kg/m² and between 30 to <40 kg/m²; 3.) Any chronic medical condition requiring pharmacologic therapy; 4.) Transaminases (AST or ALT) > 2.5 x upper limit of normal; 5.) Total bilirubin > 1.5 x upper limit of normal; 6.) Positive urine pregnancy test (if female); 7.) Abnormal electrocardiogram as judged by the study physician; 8.) Unable to tolerate venipuncture and multiple blood draws; 9.) Clinically
significant abnormal physical examination defined as a physical finding requiring further clinical
work-up; 10.) Unable to independently provide a written informed consent.

Sample size and subject matching criteria. Nine morbidly obese male and female subjects (BMI
≥ 40 kg/m²) were recruited first. Each morbidly obese subject was matched to a non-obese
subject (BMI 18.5-29.9 kg/m²) based on age (± 5 years), sex, and ideal body weight (± 4.6 kg, i.e.
± 5.08 cm in height) (10).

Pharmacokinetic sampling and bioanalysis. A single 200 mg intravenous dose (1-hour infusion)
of tedizolid phosphate (Sivextro®) was administered with subsequent collection of 11 blood
samples per subject over 72 hours. The exact sampling time-points included time-0 hour (within
30 minutes of dosing), 0.5, 1, 2, 4, 6, 8, 12, 24, 48, and 72 hours after the start of infusion. Blood
sampling was performed through a peripheral venous catheter in the arm contralateral to the
site of drug infusion. The study subjects were discharged from the clinical research unit after
the 12 hour sample, and returned to the site for subsequent sampling by peripheral venous
collection. All 5 mL blood samples were collected using K₃ EDTA blood collection tubes (BD,
Franklin Lakes, NJ, USA) to prevent ex-vivo conversion of tedizolid phosphate to tedizolid. Each
blood sample tube was inverted and made up-right 5 times to afford mixing of blood with the
anticoagulant, maintained on wet ice, and centrifuged at 1200 g for 10 minutes at 4°C within
60 minutes of collection. Plasma samples were stored frozen at -70°C until bioanalysis. Sample
analysis was performed by a validated method at Covance Laboratories (Madison, WI) as
previously described (8). Briefly, tedizolid phosphate and tedizolid were assayed by tandem-
liquid chromatography mass-spectrometry using labeled versions of both analytes as internal
standards. The curve range of detection was 0.005 mg/L to 1 mg/L, and a maximum dilution
A factor of up to 50-fold was validated for both tedizolid and tedizolid phosphate. The intra-day assay precision relative standard deviation was 2.2% to 9.1% across the low- (0.015 mg/L), mid- (0.150 mg/L), and high- (0.750 mg/L) quality control tedizolid concentrations with a mean accuracy range of 99.2% to 107%. The inter-day assay precision relative standard deviation was 5.1% to 7.0% quality control tedizolid concentrations with a mean accuracy range of 97.7% to 105%.

**Pharmacokinetic and statistical analyses.** Non-compartmental pharmacokinetic analysis (NCA) was performed using Phoenix® WinNonLin® Version 6.4 (Mountain View, CA) given the data rich nature of the sampling schema. The following parameters were derived by NCA: maximum concentration ($C_{\text{max}}$), time of maximum concentration ($T_{\text{max}}$), last measurable concentration ($C_{\text{last}}$), time of last measurable concentration ($T_{\text{last}}$), area under the curve from time zero to last measurable concentration ($\text{AUC}_{0-\text{last}}$), area under the curve from time zero to infinity ($\text{AUC}_{0-\text{inf}}$), volume of distribution during terminal phase after intravenous administration ($V_z$), clearance (CL), and terminal half-life. Between group comparisons of these matched subjects was performed using the Wilcoxon matched-pairs signed-rank test and Fisher’s Exact Test for categorical variables. Visual inspection of the scatter plot matrix, Pearson’s correlation (R), and ordinary least squares regression were used to assess the relationships between pharmacokinetic system parameters (CL, Vz) and body size. In addition, non-linear regression (power function) was used to compare pharmacokinetic system parameters to weight ($\beta$) and $\alpha\cdot(\text{weight}/\text{median weight})^{\beta}$. Discrimination between models was performed based on the coefficient of determination ($R^2$) and the Akaike Information Criterion (AIC). All statistical analyses were implemented through STATA SE, version 13.1.
RESULTS

Subject demographics. A total of 19 subjects were enrolled into the study with one withdrawal due to an intravascular infiltration during infusion of the dose. Demographic data based on the body size categorical group are summarized in Table 1. As expected based on the study inclusion criteria, the mean body weight and body mass index were approximately 1.62 fold higher in the morbidly obese compared to the non-obese group. In addition the mean body surface area was 1.27 fold higher in the morbidly obese compared to the non-obese group.

Tedizolid phosphate concentration-time profile. Tedizolid phosphate concentrations were measurable in all subjects at mid-point and end of the infusion but only measurable in 3 non-obese subjects and 1 morbidly obese subject at the 2-hour time point. The mean (standard deviation) tedizolid phosphate concentration at the end of infusion was 1.73 (0.775) mg/L and 0.909 (0.417) mg/L that was significantly higher \((p=0.0041)\) in non-obese compared to the morbidly obese group, respectively. However, this potential difference was not relevant by the 2-hour time point given that the majority of subjects had concentrations below the LLOQ. The limited detection of tedizolid phosphate concentrations in plasma is consistent with the expectation of rapid conversion in plasma to tedizolid. Given the limited measurement profile of tedizolid phosphate, pharmacokinetic analyses was not performed.

Tedizolid concentration-time profile. Tedizolid concentrations were measurable in all subjects and followed a mono-exponential decline after the end of infusion. The mean and standard deviation concentration-time profile of tedizolid is illustrated by the non-obese and morbidly obese groups (Fig. 1). As shown in this figure, mean concentrations were numerically higher initially in non-obese subjects relative to the morbidly obese subjects. However, no significant
differences were observed between the \( C_{\text{max}} \), \( T_{\text{max}} \), \( C_{\text{last}} \), or \( T_{\text{last}} \) measurements between the two groups (Table 2). The 200 mg dosage of tedizolid phosphate is equivalent to 164.5 mg of tedizolid, and so this value was used to define the tedizolid dose (100% conversion assumed). The median (range) values for the pharmacokinetic system parameters and measures of exposure are also included in Table 2. No statistically significant differences were observed between the groups. The rapid decline in tedizolid phosphate concentrations by 2 hours corresponded with a mean time to maximum concentration of 1.98 h and 1.42 h in non-obese and morbidly obese subjects, respectively (\( p=0.214 \)).

**Relationship of tedizolid pharmacokinetic parameters to body size.** The relationship of tedizolid CL to age, height, weight, ideal body weight (IBW), adjusted body weight (ABW), lean body weight (LBW), BMI, and body surface area (BSA) was assessed visually through scatter plots and linear correlation (10-13). Scatter plots of the relationships between CL, \( V_z \) and weight are illustrated in Fig. 2. Based on the review of these scatter plot, a potential outlier (178 kg individual) could serve as a leverage point and so inclusion and exclusion of this subject was tested for impact on the observed relationships. Inclusion and exclusion of this outlier had no impact on the intercept or slope of the relationships between these parameters (data not shown). Non-linear regression of CL to weight\(^{\beta} \) revealed a mean [95% confidence interval] \( \beta \) coefficient of 0.396 [0.370, 0.422], AIC = 66.3. The relationship of CL to \( \alpha \cdot (\text{weight}/95.5)^{\beta} \) was also tested but the AIC (68.2) was not improved. Regression of \( V_z \) to weight\(^{\beta} \) revealed a mean [95% confidence interval] \( \beta \) coefficient of 0.996 [0.971, 1.02], AIC = 166. However in this case, the relationship of tedizolid \( V_z \) to weight based on the function \( \alpha \cdot (\text{weight}/95.5)^{\beta} \) was improved, AIC = 160. The mean [95% confidence interval] \( \alpha \) coefficient was 101 [91.0, 110] and \( \beta \)
coefficient of 0.527 [0.197, 0.858]. Tedizolid CL had a similar correlation with BSA (R=0.530), ABW (R=0.530), LBW (R=0.521), and weight (R=0.503). Similarly, Tedizolid Vz also demonstrated a good correlation to BSA (R=0.684), ABW (R=0.714), LBW (R=0.753), and weight (R=0.646).

Safety and tolerability. Three subjects experienced four adverse events in total. One subject experienced an intravenous infiltration during the infusion. No action was required as the infusion was terminated as soon as the adverse event was observed. Given the interruption in the infusion and inability to define the dose received the subject was withdrawn from the study after resolution of the adverse event. A subject experienced a headache that resolved with self-administration of ibuprofen. This subject also experienced six episodes of diarrhea that self-resolved by the end of the study visit. These two adverse events were judged by the study physician to be probably related to the study drug. Finally, one subject experienced an ankle injury secondary to a fall with no loss of consciousness. This event was self-managed by the subject and deemed unrelated to the study drug.

DISCUSSION

This is the first study to directly compare the pharmacokinetics of tedizolid in morbidly obese and non-obese adults. The study was performed to ascertain whether a dose adjustment of tedizolid phosphate is necessary in morbidly obese adults to achieve comparable tedizolid exposures compared to non-obese adults. The study was designed to match subjects by age, sex, and ideal body weight (i.e. height) because previous analyses suggested that ideal body weight was the optimal body size predictor of tedizolid pharmacokinetic system parameters. This study demonstrates that morbidly obese subjects matched by these criteria have non-
significant differences in tedizolid exposure despite having a 62.2% higher mean body weight compared to non-obese subjects. Validation of this POP-PK expectation through this independent study and evaluation is important because it helps to ensure that a fixed dosing recommendation for tedizolid is reasonable across the wide adult patient weight range.

The plasma concentration-time profile of tedizolid was similar in the non-obese and morbidly obese subjects. As expected with most drugs, the plasma C\text{max} was numerically lower in morbidly obese subjects due to an expected increase in the volume of distribution. Analysis of the relationship of tedizolid V\text{z} with body size clearly demonstrated a linear relationship (not proportionate) with body weight. Most important, tedizolid V\text{z} was shown to scale linearly with body weight and had a $\beta$ value of 1.0, which meets the allometric expectation. Previous analyses identified central compartment volume to be a function of IBW with a $\beta$ value of 1.32. This finding is consistent with this study because IBW is a function of height and sex and is related to weight as a supra-linear function. Ultimately, less than 37% of interindividual variability of tedizolid V\text{z} was explained by body weight. In simpler terms, a 65 kg and 130 kg subject would be expected to have a V\text{z} of 83.4 L and 118 L, respectively, which is a 26.3% difference despite a 2-fold difference in body weight. Given that the pharmacodynamic effects of tedizolid are not known to be correlated to C\text{max}, the practical implications of weight on V\text{z} would be limited.

Similarly with this single dose study, the mean AUC was approximately 20% lower in the morbidly obese subjects but this difference is not statistically significant. These results are consistent with the demonstration that tedizolid clearance scales with weight$^8$, such that the
mean β value is close to 0.4. Body surface area is a function of height and weight with a β exponent of 0.425 for the Du Bois-Du Bois equation and a value of 0.5 by Mosteller’s adaptation (13, 14). An explanation of the mathematical similarity of ABW, LBW, and BSA as scalars has been detailed previously (15). Overall, body size explained less than 30% of the interindividual variability in tedizolid CL. A three-fold increase in weight would be expected to result in a 55% ($3^{0.4}$) increase in tedizolid CL. Using the linear regression equation with a recognized poor coefficient of determination (Fig 2), the estimated tedizolid CL is 5.13 L/h and 7.01 L/h in a 65 kg and 130 kg individual, respectively. Use of the power function (Fig 2) yields a 31.6% difference in tedizolid CL estimates, when comparing a 130 kg to a 65 kg individual. The predicted 30%-40% difference in CL when comparing individuals that are 2-fold different in body weight is small. Again, lower tedizolid plasma AUC may be expected with fixed dosing in a 130 kg individual but this difference is relatively small. Most importantly, the interindividual variability of tedizolid AUC was relatively small when compared to linezolid. The mean (% coefficient of variation) $AUC_{0-\infty}$ was 29.7 h•mg/L (35.3%) that was similar in variability when comparing the morbidly obese (29.3%) to the non-obese (37.2%) groups.

The findings of this study are subject to the limitations of its design. This study evaluated healthy volunteers. The effects of acute illness caused by infection, and the influence of comorbidities such as diabetes on the pharmacokinetics of tedizolid could not be determined. This study did not include elderly adults and most of the subjects were female. Given that female subjects are shorter than males on average the weight of morbidly obese subjects was predominantly below 130 kg (to meet BMI criteria) and limits definitive extrapolations above this value. The pharmacokinetics of a single intravenous dose of tedizolid was studied and so
the potential for pharmacokinetic differences in the oral bioavailability of tedizolid was not determined. Previous studies demonstrated limited systemic accumulation of tedizolid suggesting similar concentration-time profiles with single and multiple doses. Given a convergence in the concentration-time profile at 24 hours (Fig. 1) in both groups, the failure to study multiple doses is likely to be a minor limitation. Finally, additional samples should have been collected between the end of infusion and 2 hours in order to characterize the pharmacokinetics of the parent compound (tedizolid phosphate).

Despite the aforementioned limitations, important conclusions can be drawn from this work. No significant differences in the plasma exposures ($C_{\text{max}}$, $AUC_{0-\text{last}}$, $AUC_{0-\text{inf}}$, $C_{\text{last}}$) of tedizolid were observed among morbidly obese adults compared to age-, sex-, and ideal body weight-matched non-obese adults receiving a single 200 mg dose of intravenous tedizolid phosphate. Tedizolid CL and Vz correlated with body size but the absolute differences in these parameters when comparing morbidly obese and non-obese subjects is small. Specifically, this analysis suggests that less than 30% of the interindividual variability in tedizolid CL is explained by body size. The results of previous analyses documenting a potentially lower response rate in obese diabetic patients are not likely a result of altered systemic exposure. This study confirms the findings of POP-PK analyses that a tedizolid dose adjustment is not necessary in morbidly obese adults.

Acknowledgements

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References


Table 1. Summary of median (range) population demographics parameters of the non-obese and morbidly obese subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-Obese (n=9)</th>
<th>Morbidly Obese (n=9)</th>
<th>P-value</th>
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<tr>
<td>Age (years)</td>
<td>37 (24-46)</td>
<td>38 (26-50)</td>
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<tr>
<td>Height (cm)</td>
<td>164 (144-182)</td>
<td>160 (154-185)</td>
<td>0.953</td>
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<tr>
<td>Weight (kg)</td>
<td>72.6 (58.9-89.5)</td>
<td>117 (102-176)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27.4 (25.4-29.1)</td>
<td>43.5 (40.4-51.8)</td>
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<td>BSA (m²)</td>
<td>1.82 (1.57-2.09)</td>
<td>2.26 (2.12-3.01)</td>
<td>0.008</td>
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<td>IBW (kg)</td>
<td>56.4 (37.5-77.6)</td>
<td>52.4 (47.2-79.9)</td>
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Table 2. Median (range) tedizolid plasma pharmacokinetic parameters of non-obese and morbidly obese subjects

<table>
<thead>
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<th>Parameter</th>
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<th>Morbidly Obese</th>
<th>P-Value</th>
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<tr>
<td>C_{max} (mg/L)</td>
<td>2.96 (2.16-5.27)</td>
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<td>T_{max} (h)</td>
<td>1.93 (0.917-3.98)</td>
<td>1.08 (0.917-2.00)</td>
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<td>C_{last} (mg/L)</td>
<td>0.017 (0.007-0.055)</td>
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<td>T_{last} (h)</td>
<td>71.8 (48.8-73.0)</td>
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<td>AUC_{last} (h•mg/L)</td>
<td>27.2 (22.4-56.0)</td>
<td>26.0 (18.0-42.0)</td>
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<td>AUC_{inf} (h•mg/L)</td>
<td>27.4 (22.7-57.0)</td>
<td>26.3 (18.4-43.2)</td>
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<td>CL (L/h)</td>
<td>5.99 (2.88-7.25)</td>
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<td>V_{z} (L)</td>
<td>88.2 (53.3-124)</td>
<td>101 (76.8-150)</td>
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<td>Half-Life (h)</td>
<td>11.7 (9.00-15.0)</td>
<td>11.9 (8.01-14.1)</td>
<td>0.953</td>
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Figure 1. Mean and standard deviation (SD) error bars of the tedizolid plasma concentration-time profile by non-obese and morbidly obese subjects.
Figure 2. Scatter, linear, and power function regression plots with equations and coefficient of determination for tedizolid (A) clearance and body weight and (B) volume of distribution and body weight.
CL = 3.241 + 0.029 x (Weight), R^2 = 0.204 (Linear Function)
CL = (Weight)^0.396, R^2 = 0.944 (Power function)

Tedizolid Plasma Clearance (L/h)

Weight (kg)

50 75 100 125 150 175 200
Vz = 101 \times \frac{\text{Weight}}{95.5}^{0.527} \quad \text{R}^2 = 0.964 \quad \text{(Power Function)}

Vz = 49.1 + 0.529 \times \text{Weight} \quad \text{R}^2 = 0.369 \quad \text{(Linear Function)}

Tedizolid Plasma Volume of Distribution (L)

Weight (kg)

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