Pharmacokinetics of Intravenous Linezolid in Moderately to Morbidly Obese Adults

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The pharmacokinetics of linezolid was assessed in 20 adult volunteers with body mass indices (BMI) of 30-54.9 kg/m² receiving 5 intravenous doses of 600mg every 12h. Pharmacokinetic analyses were conducted using compartmental and non-compartmental methods. Mean ± standard deviation age, height, and weight were 42.2±12.2 yrs, 64.8±3.5 in, and 109.5±18.2 kg (range: 78.2-143.1 kg), respectively. Linezolid pharmacokinetics in this population were best described by a 2-compartment model with non-linear clearance (original value: 7.6 ± 1.9 L/hr), which could be inhibited to 85.5 ±12.2% of its original value depending on the concentration in an empirical inhibition compartment, volume of the central compartment (24.4 ± 9.6 L), and intercompartment transfer constants (k₁₂ and k₂₁) of 8.04 ± 6.22 and 7.99 ± 5.46 h⁻¹, respectively. Area under the curve for the 12 hour dosing interval (AUCₜ) was similar between moderately obese and morbidly obese groups: 130.3 ± 60.1 versus 109.2 ± 25.5 µg*h/mL, p=0.32, and there was no significant relationship between AUC or clearance and any body size descriptors. A significant positive relationship was observed for total volume of distribution with total body weight (r²=0.524), adjusted body weight (r²=0.587), lean body weight (r²=0.495), and ideal body weight (r²=0.398), but not with BMI (r²=0.171). Linezolid exposure in these obese participants was overall similar to that of non-obese patients, implying that dosage adjustments based on BMI alone are not required, and standard doses for patients with body weights up to approximately 150 kilograms should provide similar AUCₜ as seen in non-obese participants.
INTRODUCTION

Over 78 million United States adults were defined as obese in 2009-2010 using the WHO BMI classification system, thus it is evident that obesity has become a substantial health problem (17). Not only is obesity associated with a number of co-morbidities such as hypertension, diabetes, and cardiovascular disease, but it has also been identified as an independent risk factor for infection and is often associated with worse clinical outcomes (18, 20, 26). As a result, adequate antimicrobial exposure is essential to ensure treatment success. Unfortunately, data surrounding the pharmacokinetics and dosing recommendations of many antimicrobials in obese patients are sparse. Changes in volume of distribution and clearance in obese patients can significantly impact drug concentrations (2). The degree of alteration depends on various factors such as the extent of obesity and the physical and chemical properties of the drug. For example, volume of distribution in obese patients may vary depending on the amount of adipose tissue present and the lipophilic properties of the antibiotic; such increases in volume of distribution could result in low serum concentrations. Clearance may also be altered in the obese population, particularly for molecules that are eliminated through renal excretion pathways. Finally, alterations in hepatic enzymes can occur as a result of increased fatty liver deposits.

Linezolid, an oxazolidinone antibiotic, is often utilized for infections commonly seen among obese patients, such as skin and soft tissue infections including diabetic foot infections (27). The current recommended dose is 600 mg every 12 hours intravenously (IV) or orally (27). There are no weight based recommendations or guidelines for dosing linezolid in obese patients. However, there is some evidence from case reports and small studies with sparse blood sampling that concentrations may be lower in obese patients, thus requiring dosage increases (7, 16, 23, 24).
The objective of this study was to determine the pharmacokinetics of linezolid 600 mg IV every 12 hours in moderately and morbidly obese adult bariatric patients as defined by body mass index (BMI) and determine the relationship between several body size descriptors in this population and individual pharmacokinetic parameters.

MATERIALS and METHODS

Study Protocol. This was a prospective, open-label, pharmacokinetic study in 20 obese adult participants. Participants were enrolled through the Center for Metabolic and Bariatric Surgery at Hartford Hospital and divided evenly into one of two BMI groups. Ten participants were classified as moderately obese (Class I and II obesity, BMI = 30-39.9 kg/m²) and ten participants were classified as morbidly obese (Class III obesity, BMI ≥ 40 kg/m²). The study protocol was reviewed and approved by the Institutional Review Board at Hartford Hospital, and written informed consent was obtained prior to the study. All participants were admitted to the Clinical Research Center at Hartford Hospital for the 5 day study period.

Participants. Adults who were at least 18 years old were screened for enrollment after providing informed consent. Screening included a medical history, physical examination, blood pressure, pulse, temperature, and evaluation of clinical laboratory data (complete blood count with differential, serum electrolytes, blood urea nitrogen, serum creatinine, liver function panel, urinalysis with microscopy, and urine β-human chorionic gonadotropin hormone for female subjects). Participants were excluded if they had a known allergy to linezolid or any other oxazolidinone antibiotic; were pregnant or breast feeding; had BMI greater than or equal to 55 kg/m²; clinically abnormal aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphate, total bilirubin, hemoglobin, platelet, or white blood cell count; serum
creatinine greater than 1.5 mg/dL, or creatinine clearance (CrCL) < 50 ml/min, as calculated by Cockroft-Gault using adjusted body weight; blood pressure greater than or equal to 140 mm Hg systolic or 90 mm Hg diastolic on a single measurement; receiving monoamine oxidase inhibitors or serotonergic agents such as selective serotonin reuptake inhibitors; an active, ongoing infection that requires receipt of systemic antibiotics, antivirals or antifungals, Human Immunodeficiency Virus (HIV), any malignancy that requires treatment, history of solid organ or bone marrow transplantation; history of regular alcohol consumption; use of tobacco or nicotine containing products; or a positive urine screen for drugs of abuse.

**Study medication.** Linezolid for injection (lot 10K18U17, expiration 11/2013) 600 mg single-use, premixed infusion bags were provided by Pfizer, Inc. (New York, NY). All doses were protected from light and stored at room temperature. Participants received five doses of IV linezolid 600 mg every 12 hours. All doses were infused over 30 minutes using a programmed infusion pump through a peripheral IV catheter (Jelco™, Smiths-Medical, Southington, CT). Each dose was preceded by a 1 h fast and followed by a 2 h fast.

**Sample collection.** Blood samples were collected from a midline catheter placed in the arm opposite from the dosing catheter. Samples were collected at 0 (start of the infusion), 0.5 (end of the infusion), 0.75, 1, 2, 3, 4, 6, 8, 12, 18, and 24 h following the fifth dose administered. Blood samples were collected using a 10 mL red top BD Vacutainer (Becton, Dickinson and Company, Franklin Lakes, NJ). Samples were centrifuged to obtain separated serum. Serum samples were immediately frozen and stored at -80°C until analysis.

**Protein binding.** Protein binding was assessed in triplicate for each participant at the time of the estimated peak concentration (0.5h). Briefly, a blood sample was collected into a 10 mL BD Vacutainer and centrifuged to obtain separated serum. An aliquot of 0.9 mL of serum was
transferred into three regenerated cellulose 30 kDa molecular weight cutoff ultrafiltration devices
(Centrifree Centrifugal Filters, Millipore Corporation, Billerica, MA) and centrifuged at 2,000 x
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g using a fixed angle rotor for 45 minutes at 10°C to obtain ultrafiltrate (C_{ultrafiltrate}). An aliquot
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of serum was also retained at each corresponding time point for total drug concentration
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determination at that time point (C_{total}). Protein binding was calculated using the following
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equation: \% protein binding = 100 – (100 \times C_{ultrafiltrate}/ C_{total}).

**Analytical procedures.** Linezolid concentrations in serum and ultrafiltrate were determined
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using a validated high-performance liquid chromatography (HPLC) assay at the Center for Anti-
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Infective Research & Development in Hartford, CT based on a previously published assay (5).
The serum assay was linear over a range of 0.2 to 30 µg/mL (r^2 = 1.00) For serum, the mean
123
interday coefficient of variability for the high (20 µg/ml) and low (0.5 µg/ml) quality control
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samples were 4.4% and 3.8%, respectively; whereas, the respective mean intraday coefficient of
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variability were 3.3% and 2.4%. The ultrafiltrate assay was linear over a range of 0.1 to 20
126
µg/mL (r^2 = 0.998). For ultrafiltrate, the mean interday coefficient of variation for high (15
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µg/ml) and low (0.2 µg/ml) check samples were 1.3% and 1.8%, respectively. The mean
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intraday coefficients of variation were 1.4% and 2.0%, respectively.

**Noncompartmental pharmacokinetic analysis.** The observed area under the concentration
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time profile from 0 to 12h at steady state (AUC_t) was calculated using the linear-log trapezoidal
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method. The maximum concentration of linezolid (C_{max}) was determined by visual inspection of
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the concentration time profile.

**Population Pharmacokinetics.** Concentration data were modeled by non-parametric
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adaptive grid (BigNPAG) with adaptive \( \gamma \) as described by Leary and colleagues (13). One and
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two compartmental models with linear and non-linear clearance were assessed. Non-linear
models included parallel capacity-limited (non-renal) and first-order (renal) clearances (15), as well as non-linear clearance that can be inhibited over time depending on the concentration in an empirical inhibition compartment (19). The final model was selected based on the log likelihood, Akaike information criterion, and the ability to accurately predict the observed hour area under the curve after the 5th dose. Weighting based on intra-day assay variance was employed using a plot of the assay standard deviation (SD) versus measured linezolid concentration, which was best described by the equation \( \text{SD} = \gamma(0.00189 + 0.0412*\text{C}) \), where \( \text{C} \) is the linezolid concentration and \( \gamma \) was identified as 2.085. Mean values were used as the measure of central tendency for population parameter estimates. Bayesian estimates were obtained for each patient using the population-of-one utility within BigNPAG. The mean weighted error was the estimate of bias. The bias-adjusted mean weighted squared error was employed as the estimate of precision. \( \text{AUC}_{\tau} \) was calculated for each participant by simulating the concentration time profile after 5 doses of linezolid 600mg every 12 hours using ADAPT 5.

**Statistics.** Pharmacokinetic parameter estimates were compared between BMI groups using a t-test or Mann-Whitney Rank Sum test if data failed a normality test (Sigma Stat, SPSS, Chicago, IL). A p-value of 0.05 was considered statistically significant. Body size descriptors [ideal body weight (IBW), lean body weight (LBW), total body weight (TBW), adjusted body weight (adjBW), and BMI] were analyzed for correlation with clearance (CL), volume of the central compartment (Vc), and total volume of distribution (Vd) [the sum of Vc and the calculated volume of the peripheral compartment (Vp)] derived from the final population pharmacokinetic model for all participant data using linear regression. AdjBW in kilograms (kg) was calculated as \( \text{IBW} + 0.4(\text{TBW} – \text{IBW}) \) (2). IBW was calculated as described by Devine and
IBW (kg) = 45.4 (49.9 if male) + 0.89 x (height in cm – 152.4) (9). LBW in kilograms was calculated by the methods of Janmahasatian and colleagues, LBW (males) = [9270 x TBW] / [6680 + (216 x BMI)]; LBW (females) = [9270 x TBW] / [8780 + (244 x BMI)] (11).

**Safety.** Adverse event monitoring took place throughout the entire study. An adverse event was defined as any pathologic or unintended change in the structure (signs), function (symptoms), or chemistry (laboratory values) of the body associated with the use of linezolid, whether or not it was considered drug related.

**RESULTS**

**Participants.** A total of four males and sixteen females were enrolled in the study and all 20 participants completed the study. Demographics and values of body size are presented in Table 1.

**Protein Binding.** The mean ± standard deviation protein binding was 13.1 ± 8.9 %. There was no difference in protein binding between the two BMI groups (14.2 ± 9.1 versus 12.0 ± 9.1 %, p=0.595). Protein binding ranged from 0.0 to 30.7% over a total drug concentration range of 10.25 to 30.48 µg/mL. The protein binding was not observed to be concentration dependent.

**Noncompartmental Pharmacokinetic Analysis.** There was no difference in AUC\(\tau\) or \(C_{\text{max}}\) between moderately and morbidly obese BMI groups (Table 2).

**Population Pharmacokinetic Analysis.** A two compartment model with non-linear clearance and an empirical inhibition compartment fit the data best. Final population estimates are provided in Table 3. This model includes a non-linear inhibition term (RCLF) that represents the fraction of CL that cannot be inhibited (Fig 1). For example, the mean RCLF of 0.855
signifies that clearance can be inhibited to 85.5% of its original value over time. Fig. 2a demonstrates the observed versus population predicted plots (using the mean parameter vector) for linezolid concentrations in serum. The measures of bias and precision were acceptable for a pre-Bayesian analysis. A single participant from the lower BMI group had observed linezolid concentrations significantly greater than the rest of the population. Removing this patient’s concentration data resulted in mean population parameter estimates that were within 5% of the total population estimates, therefore, this participant’s data were retained in the analyses. Fig. 2b demonstrates the observed versus individual Bayesian predicted plots, which had a $r^2$ of 0.98 and excellent bias and precision.

Model predicted AUC$_\tau$ after the 5th dose was 118.3 ± 45.3 µg*h/mL, which was in agreement with the observed AUC$_\tau$ from the non-compartmental analyses. For the moderately obese BMI group (30-39.9 kg/m$^2$), the model predicted AUC$_\tau$ was 128.2 ± 58.7 µg*h/mL; this value was 110.3 ± 17.2 µg*h/mL after removing the single patient with very high concentrations. For the morbidly obese BMI group (40-54.9 kg/m$^2$), the model predicted AUC$_\tau$ was 108.5 ± 25.7 µg*h/mL. There was no difference in CL, Vc, Vd, or RCLF between BMI groups (Table 4).

There was no significant relationship between total body weight and the observed AUC$_\tau$ exposure (Fig 3). Finally, the relationship between CL, Vc, and Vd with body size descriptors is listed in Table 5. Only total Vd was associated with TBW, LBW, AdjBW, and IBW, but not with BMI.

**Safety.** Linezolid was well tolerated with no serious adverse events. Adverse events reported were mild with the most common being headache ($n=11$) and increased gas/flatulence ($n=5$). One participant experienced a yeast infection after completion of the study, which resolved after systemic treatment with fluconazole. Two participants experienced slight
reductions in hemoglobin from baseline. Upon repeat laboratory testing, hemoglobin levels recovered to within normal range.

DISCUSSION

Obesity can lead to altered pharmacokinetic parameters which can impact antimicrobial exposures (2). Insufficient exposures can result in treatment failures and increase the risk of resistance. Increasing the dose to compensate for presumed insufficient exposures, however, can lead to toxicity, thus it is important to have systematic data on the changes in pharmacokinetics, if any, as body weight increases so that informed dosing selection can be made. This study systematically evaluated the pharmacokinetics of 10 moderately obese and 10 morbidly obese participants. Linezolid pharmacokinetics in this obese population were well characterized by a 2 compartment model with non-linear clearance. Among these obese, un-infected participants, there was no difference in pharmacokinetic parameters or AUC exposures for the standard linezolid regimen of 600mg every 12 hours; however, a significant relationship between weight and total volume of distribution was observed.

The pharmacodynamic parameter of importance for linezolid activity is the AUC/MIC ratio (1), thus assessing changes in AUC exposure by body size is of paramount importance. Observed steady-state AUC exposures for the 12 hour dosing interval in these obese participants was not different between BMI groups. Moderately obese patients with a BMI of 30-39.9 kg/m² achieved AUCₜ exposures of 130.3 ± 60.1 μg*h/mL, while morbidly obese patients with a BMI of 40-54.9 kg/m² achieved AUCₜ exposures of 109.2 ± 25.5 μg*h/mL (p=0.32). The numeric difference in AUCₜ exposure between the groups was largely due to one 89 kg female participant with a BMI of 36.2 kg/m². This participant’s observed AUCₜ was 294.25 μg*h/mL, and when
removed from the average calculation, the mean AUC\(\tau\) for the moderately obese group fell to 112.10 ± 18.4 µg*h/mL. The C_{max} for moderately and morbidly obese participants were also not different at 20.9 ± 5.0 and 18.8 ± 2.6 µg/mL (p=0.237), respectively. When compared with data in non-obese healthy volunteers who received multiple doses of 625mg IV every 12 hours (22), the steady-state AUC_{0-12} (93.4 ± 32.3 µg*h/mL) and C_{max} (15.7 ± 2.6 µg/mL) exposures were numerically lower for the non-obese population. Among 95 obese (defined as TBW >30% above IBW) patients treated in the linezolid compassionate use program, steady-state AUC_{0-12} was approximately 105 ± 28 µg*h/mL, and was similar to the total population of patients (AUC_{0-12}: 114 ± 29 µg*h/mL) (15).

Previously published data have reported lower linezolid concentrations in obese patients (7, 16, 23, 24). One study with seven obese patients receiving oral linezolid 600mg every 12 hours for cellulitis (23) compared a one hour linezolid concentration of 12.3 µg/mL in their patients with previously reported peak concentrations of 16.3 to 24 µg/mL in non-obese patients (6, 14). The mean weight of the patients (146 ± 37 kg) included in this study was greater than that of our population, and all patients had a total body weight >50% of their ideal body weight. While the observed one hour concentration in the study was low, it is possible that a true peak was missed given the sparse sampling design (i.e., samples were obtained only at 1, 6, and 12 h) and because linezolid was administered orally. The sparse sampling would have also affected the reported AUC\(\tau\) in the study, which was 92 ± 33 µg*h/mL. A second study determined linezolid pharmacokinetics in nine critically ill patients receiving normal to high doses of intravenous linezolid ranging from 600mg every 12 h to 900 mg every 8 h (7). The mean TBW and BMI of these patients were 174 ± 19 kg and 53.8 ± 7.9 kg/m², respectively. Once again, sparse sampling was employed with the earliest concentration determined 1-3 hours after completion of the
infusion and a second concentration collected at the trough; a peak was estimated by back
extrapolating assuming 1-compartment linear pharmacokinetics. After normalizing to a dose of
600 mg every 8 h, the investigators report a 24 hour AUC in these patients of 211 ± 102 µg*h/mL. For comparison, a steady-state 24 hour AUC for 600mg every 8 hours using our mean population pharmacokinetic parameters results in a value of 324 µg*h/mL. Again, there may be several reasons, unrelated to obesity, why AUC exposure for such a dosing regimen would be lower in the second study’s population. The investigators assumed a one-compartment, linear model when estimating the peak concentration and AUC exposure, thus the true peak may have been underestimated, and clearance would be reduced over additional days of therapy. Secondly, the study population was infected, critically ill patients. The physiological stress of critical illness can most certainly impact pharmacokinetics of antibiotics (10, 21, 25). Several pharmacokinetic studies for linezolid have been conducted in critically ill patients (4, 15, 19), and Meagher and colleagues identified that critically ill patients may have approximately a 60% increase in clearance, thus resulting in lower AUC values (15).

Like other studies, linezolid concentrations in this obese population of bariatric patients fit a 2 compartment model with non-linear clearance (3, 12, 15, 19). Based on log-likelihood and Akaike Information Criteria, the model originally described by Plock and colleagues (19) resulted in the best fit of the data. This was despite the absence of concentration data after the first linezolid dose. Compared with the healthy volunteers and critically ill patients included in the original Plock paper, our clearance (7.6 L/hr) was lower than their reported value of 11.1 L/hr. Additionally, their estimate for RCLF (0.764) was lower than our mean of 0.855. When one considers that the reported clearance in this model is the maximum initial clearance and then is reduced by the fraction of RCLF, the mean population clearance reported by Plock and
colleagues is reduced to 8.48 L/hr over time and our obese population is reduced to 6.5 L/hr.
Both values are among those reported in other linezolid pharmacokinetic studies (3, 6, 12, 15, 22). Thus, it can at least be determined based on these data that the obese bariatric patients in our study do not have higher clearance and reduced AUC exposure compared with other studies. This is further substantiated by the lack of significant relationship between clearance and any of the body size descriptors (Table 5). The volume of the central compartment described by Plock (20.0 L) was also similar to our observed value of 24.4 L. Notably, there was also no significant association between any of the body size descriptors and Vc. However, when analyzing body size descriptors relative to total volume of distribution, a significant association was present for all descriptors except BMI. This is notable since one’s level of obesity is defined by weight in relation to height (i.e., BMI), but BMI alone does not appear to be an important predictor for pharmacokinetic parameters. The association observed between body weight and linezolid’s total volume of distribution is worth pursuing further for clinical significance.

In summary, these data demonstrate that standard doses of linezolid 600mg every 12 hours in individuals weighing up to approximately 150 kilograms should provide similar AUCτ exposures to non-obese patients. Additionally, BMI is a poor predictor for adjusting dosing regimens in the obese population, and a more accurate descriptor of body mass should be utilized. Finally, a correlation between Vd and several body weight descriptors was observed suggesting that concentrations in patients weighing greater than the participants included in this study may be altered as described by previous studies.
ACKNOWLEDGEMENTS

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REFERENCES:


FIG 1. Two compartment structural model used to fit linezolid concentration data. Clearance (CL) is inhibited based on the concentration in an empirical inhibition compartment. A3 corresponds to the concentration in the inhibition compartment so that $\text{INH} = [\text{RCLF} + (1 - \text{RCLF}) \times ((1 - A3)/(\text{IC}_{50} + A3))]$; Vc, volume of central compartment; Vp, volume of peripheral compartment; $K_{12}$, intercompartment transfer constant; $K_{21}$, intercompartment transfer constant; $K_{IC}$, rate constant into inhibition compartment; RCLF, remaining CL fraction (i.e., the fraction of clearance that cannot be inhibited); $\text{IC}_{50}$, concentration in the inhibition compartment yielding 50% of maximum clearance inhibition.
FIG 2 a.) Observed versus population predicted and b.) observed versus individual predicted concentrations from the final population pharmacokinetic model a.
Bayesian Estimates

$r^2 = 0.98$
Mean Weighted Error = -0.08
Bias-Adjusted Mean Weighted Squared Error = 0.996
FIG 3. AUC\(\tau\) exposures in relation to total body weight for the 20 obese participants (BMI 30.0-54.9 kg/m\(^2\)). Open circles (males), solid circles (females). The regression equation is \(y = -0.9637x + 223.8, p = 0.0923, r^2 = 0.149\).
<table>
<thead>
<tr>
<th>Variable</th>
<th>Moderately Obese (BMI: 30-39.9 kg/m²)</th>
<th>Morbidly Obese (BMI: 40-54.9 kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / Female, Number</td>
<td>4 / 6</td>
<td>0 / 10</td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>41.7 ± 13.0</td>
<td>42.6 ± 12.7</td>
</tr>
<tr>
<td>Height (inches), mean ± SD</td>
<td>65.0 ± 4.0</td>
<td>63.9 ± 3.0</td>
</tr>
<tr>
<td>TBW (kg), mean ± SD, (range)</td>
<td>98.9 ± 13.9, (78.2-123.4)</td>
<td>120.0 ± 16.1, (95.6-143.1)</td>
</tr>
<tr>
<td>AdjBW (kg), mean ± SD</td>
<td>73.6 ± 10.9</td>
<td>81.6 ± 10.1</td>
</tr>
<tr>
<td>LBW (kg), mean ± SD</td>
<td>52.0 ± 6.9</td>
<td>60.5 ± 8.7</td>
</tr>
<tr>
<td>IBW (kg), mean ± SD</td>
<td>56.7 ± 9.1</td>
<td>56.0 ± 7.3</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>36.2 ± 1.7</td>
<td>45.3 ± 3.2</td>
</tr>
</tbody>
</table>

BMI, body mass index; TBW, total body weight; AdjBW, adjusted body weight; LBW, lean body weight; IBW, ideal body weight; kg, kilogram; m, meter; SD, standard deviation
Table 2. Comparison of AUC\(_\tau\) and C\(_{\text{max}}\) between moderately obese and morbidly obese participants by non-compartmental methodology

<table>
<thead>
<tr>
<th></th>
<th>All Participants (n=20)</th>
<th>Moderately Obese (BMI: 30-39.9 kg/m(^2)) (n=10)</th>
<th>Morbidly Obese (BMI: 40-54.9 kg/m(^2)) (n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(_\tau)</td>
<td>119.8 ± 46.24</td>
<td>130.3 ± 60.1</td>
<td>109.2 ± 25.5</td>
<td>0.32</td>
</tr>
<tr>
<td>C(_{\text{max}})</td>
<td>19.8 ± 4.00</td>
<td>20.9 ± 5.0</td>
<td>18.8 ± 2.6</td>
<td>0.237</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD.

AUC\(_\tau\), AUC calculated from 0-12 h after the 5\(^{th}\) dose; C\(_{\text{max}}\), observed maximum concentration
Table 3. Population pharmacokinetic parameter estimates for the final two compartment model describing linezolid serum concentrations in 20 obese adults

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_c$ (L)</td>
<td>24.35</td>
<td>9.39</td>
<td>22.14</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>7.61</td>
<td>1.82</td>
<td>7.66</td>
</tr>
<tr>
<td>$k_{12}$ (h$^{-1}$)</td>
<td>8.04</td>
<td>6.07</td>
<td>7.82</td>
</tr>
<tr>
<td>$k_{21}$ (h$^{-1}$)</td>
<td>7.99</td>
<td>5.33</td>
<td>7.26</td>
</tr>
<tr>
<td>RCLF</td>
<td>0.855</td>
<td>0.1190</td>
<td>0.8675</td>
</tr>
<tr>
<td>IC$_{50}$</td>
<td>0.422</td>
<td>0.3790</td>
<td>0.4247</td>
</tr>
<tr>
<td>$K_{IC}$</td>
<td>0.581</td>
<td>0.4244</td>
<td>0.8599</td>
</tr>
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</table>

$V_c$, volume of distribution of the central compartment; CL, clearance; $k_{12}$, microtransfer rate constant from the central to peripheral compartment; $k_{21}$, microtransfer rate constant from the peripheral to central compartment; RCLF, remaining CL fraction; IC$_{50}$, concentration in the inhibition compartment yielding 50% of maximum clearance inhibition.
**TABLE 4.** Comparison of model predicted pharmacokinetic parameters between moderately obese and morbidly obese participants.

<table>
<thead>
<tr>
<th></th>
<th>Moderately Obese (BMI: 30-39.9 kg/m², n=10)</th>
<th>Morbidly Obese (BMI: 40-54.9 kg/m², n=10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/hr)</td>
<td>7.83 ± 1.77</td>
<td>7.39 ± 2.02</td>
<td>0.619</td>
</tr>
<tr>
<td>Vc (L)</td>
<td>26.4 ± 8.9</td>
<td>22.3 ± 10.3</td>
<td>0.358</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>44.1 ± 9.9</td>
<td>62.2 ± 40.3</td>
<td>0.089 *</td>
</tr>
<tr>
<td>RCLF</td>
<td>0.83 ± 0.13</td>
<td>0.88 ± 0.11</td>
<td>0.349</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD. CL, clearance; Vc, volume of the central compartment; Vd, total volume of distribution; RCLF, remaining CL fraction.

* This comparison failed a normality test, so analyzed by Mann-Whitney Rank Sum test.

Excluding single patient in morbidly obese group with calculated Vd of 175.9 L, the mean ± SD Vd for this group is 49.6 ± 6.0 L (p=0.170).
**TABLE 5.** Linear regression analyses for clearance (CL), volume of the central compartment (Vc), and total volume of distribution (Vd) in association with body size descriptors.

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<thead>
<tr>
<th>Body Size Descriptor</th>
<th>CL (L/hr) R²</th>
<th>p-value</th>
<th>Vc (L) R²</th>
<th>p-value</th>
<th>Vd (L) R²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBW (kg)</td>
<td>0.005</td>
<td>0.761</td>
<td>0.0006</td>
<td>0.9189</td>
<td>0.524</td>
<td>0.0005</td>
</tr>
<tr>
<td>LBW (kg)</td>
<td>0.044</td>
<td>0.375</td>
<td>0.0003</td>
<td>0.9388</td>
<td>0.495</td>
<td>0.0008</td>
</tr>
<tr>
<td>AdjBW (kg)</td>
<td>0.037</td>
<td>0.420</td>
<td>0.0048</td>
<td>0.7717</td>
<td>0.587</td>
<td>0.0001</td>
</tr>
<tr>
<td>IBW (kg)</td>
<td>0.102</td>
<td>0.171</td>
<td>0.0367</td>
<td>0.4185</td>
<td>0.398</td>
<td>0.0038</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.020</td>
<td>0.549</td>
<td>0.0393</td>
<td>0.4021</td>
<td>0.171</td>
<td>0.0785</td>
</tr>
</tbody>
</table>

TBW, total body weight; LBW, lean body weight; AdjBW, adjusted body weight; IBW, ideal body weight; BMI, body mass index

* Regression analyses for Vd excluded data from one subject with a calculated Vd of 175.9 L, approximately three fold higher than the next largest Vd. Inclusion of this patient’s data prevented any significant relationships from being observed.
Pre Bayesian Estimates

$r^2 = 0.70$
Mean Weighted Error = 0.065
Bias-Adjusted Mean Weighted Squared Error = 22.23
Bayesian Estimates

$r^2 = 0.98$
Mean Weighted Error = -0.08
Bias-Adjusted Mean Weighted Squared Error = 0.996