Oral bioavailability of linezolid before and after Roux-en-Y gastric bypass surgery: is dose modification necessary in obese subjects?

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Objectives: We characterized the pharmacokinetics of intravenous (iv) and oral linezolid before and after Roux-en-Y gastric bypass surgery (RYGBS).

Methods: Subjects with a body mass index (BMI) > 35 kg/m² received a single iv 600 mg dose of linezolid followed by the same oral dose after a 7 day washout period between doses, before and 3 months after RYGBS. Serum linezolid concentrations were measured by a validated HPLC method with ultraviolet detection. Parametric population pharmacokinetic analysis was used to evaluate bioavailability and the influence of total body weight (TBW) on pharmacokinetic parameters. The area under the serum concentration–time curve extrapolated to infinity (AUC0–∞) was compared between subjects before and after RYGBS, and with non-obese controls.

Results: Five (four male) obese subjects were studied with a mean (SD) age of 51.4 (5.01) years, TBW of 124 (10.6) kg and initial BMI of 44.9 (7.52) kg/m². The bioavailability was a mean (95% CI) of 1.14 (0.816–1.47) before and 1.14 (1.01–1.26) after RYGBS. The mean (SD) AUC0–∞ with oral linezolid before RYGBS was 41.6 (20.9) mg·h/L compared with 98.9 (24.7) mg·h/L after RYGBS (P < 0.001). This increase in AUC0–∞ corresponded with a 25.3% reduction in the TBW after RYGBS, as the TBW was a significant covariate of clearance. The probability of pharmacodynamic target attainment with standard doses of linezolid is lower in obese versus non-obese individuals.

Conclusions: The bioavailability of linezolid is not impaired by RYGBS. The serum exposure of linezolid is more than 50% lower in obese compared with non-obese subjects, suggesting that dose modification may be needed.

Keywords: oxazolidinones, pharmacokinetics, bariatric, pharmacodynamics, surgery

Introduction

The prevalence of obesity has increased globally with an estimated 26% and 36% prevalence of adults with a body mass index (BMI) > 30 kg/m² in England and the USA, respectively.1,2 An estimated 220000 bariatric surgical procedures are performed in the USA each year to permit long-term weight loss and improve glycaemic control.3 Roux-en-Y gastric bypass surgery (RYGBS) is the most common bariatric procedure that is performed to reduce the size of the stomach and bypass the absorptive segment of the duodenum.4 Although this procedure induces significant weight loss, it may alter the oral absorption of drugs.5 Therapeutic failure and decreased absorption have been described in subjects after bariatric surgery with agents such as amoxicillin, nitrofurantoin, amoxicillin/clavulanate, mycophenolic acid, sirolimus and tamoxifen.4–7 In contrast, there was no change in the absorption of temozolomide or levithyroxyne before or after RYGBS.8,9 The bioavailability of metformin and mexitofloxacin increased in subjects after RYGBS compared with that in control subjects.10,11 Given this potential for variability in oral bioavailability after RYGBS, a stepwise evaluation of key drugs should be performed and not assumed to be predictable.4–11

Linezolid represents a key orally bioequivalent drug that is used to treat Gram-positive bacterial pathogens such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus faecium (VRE) and Streptococcus species,
including multidrug-resistant strains of Streptococcus pneumoniae. The limited pharmacokinetic data from obese subjects to date suggest that this population has a lower systemic exposure of linezolid compared with non-obese controls. Population pharmacokinetic analyses have also demonstrated a correlation between body size and linezolid drug clearance. This association is concerning given that a standard fixed dose of linezolid is used in all adult subjects without regard to body size. Lower linezolid exposures in obese subjects with the use of standard doses may contribute to clinical failure and the emergence of resistance.

Given that RYGBS induces significant weight loss, evaluation of the pharmacokinetic profile of drugs like linezolid before and after RYGBS provides a unique pharmacological opportunity to assess the independent effect (subjects serve as controls) of body weight on pharmacokinetics. Thus, this study aimed to quantify the serum pharmacokinetics of oral and intravenous linezolid in obese subjects before and 3 months after RYGBS. Herein we compare the exposure profile of linezolid in obese subjects, in the same individuals after weight loss due to RYGBS, and in non-obese historic controls.

Methods

Subjects

The study was approved by the Winchester Hospital Human Studies Committee, and all subjects gave written informed consent before participation. Adults >18 years of age, BMI >35 kg/m² with serious obesity-related co-morbidities, no recent smoking habit, no active drug or alcohol abuse and the mental ability to understand the risks and benefits of surgery were included. All volunteers underwent a review of their medical history and laboratory blood panels. Volunteers were excluded if they: (i) had a known hypersensitivity or intolerance to linezolid; (ii) required use of prokinetic agents (e.g. metoclopramide or erythromycin) or serotonergic agents within 14 days of study commencement; (iii) had a history of drug or alcohol abuse during the past year; (iv) received an investigational drug or donated blood in the preceding 3 months; (v) were pregnant or attempting to become pregnant; (vi) were females nursing an infant; (vii) had active liver disease (transaminase or bilirubin values greater than three times the upper normal limits) or renal insufficiency (creatinine clearance <80 mL/min/1.73 m²); (vii) had a platelet count <150x10⁹/mm³ or haemoglobin <12 g/dL for women and <13 g/dL for men; and (viii) had previously undergone stomach or intestinal surgery.

Study design

This was a prospective, open-label, crossover, single-dose study performed before RYGBS and ~3 months after RYGBS. In each phase of the study the subjects were administered a single dose of 600 mg of linezolid (Zyvox®, New York City, NY, USA) iv over 60 min and 600 mg of linezolid orally with water, separated by at least a 7 day washout period. All doses were administered in the hospital on an empty stomach 1 h before or 3 h after a meal. Assessment of vital signs and laboratory assays (haematocrit, haemoglobin and platelet levels with blood chemistry) were performed for each volunteer prior to the start of the study. Study personnel monitored each subject for any adverse events 24 h after the administration of each dose of linezolid.

Sample collection and analysis

Blood samples (5 mL) were collected via direct venipuncture or midline indwelling catheter into a Vacuette® red top (Greiner Bio-One North America Inc., Monroe, NC, USA). Serial blood samples were collected in both phases after the single-dose administration as follows: 0 (just prior to the dose), 0.5, 1, 2, 4, 8, 12 and 24 h after the dose. Direct venipuncture was specifically used with the collection of the 0.5 and 1 h blood samples when linezolid was administered by iv infusion. All blood samples were collected in the hospital. Immediately after blood sample collection, the serum was separated from the cells by centrifugation and stored at −20°C until analysis. The serum concentrations of linezolid were assayed by Advanced Diagnostic Laboratories at National Jewish Health (Denver, CO, USA) by using a validated HPLC method. Linezolid serum concentrations were measured using a system consisting of a ThermoFinnegan P4000 HPLC pump (San Jose, CA, USA) with a model AS1000 fixed-volume autosampler, a model UV2000 ultraviolet detector, a Gateway Series e computer (Pawray, CA, USA) and the Chromquest HPLC data management system. The serum standard curve for linezolid ranged from 0.5 to 30 mg/L. The percentage coefficient of variation of a single standard concentration was 0.69%, and the overall validation precision across all standards was 1.0%–4.4%.

Population pharmacokinetic (POP-PK) model development

Parametric POP-PK systems analysis was performed using ADAPT 5, developed by David D’Argenio, Alan Schumitzky and Xiaoning Wang at the Biomedical Simulations Resource, University of Southern California. The initial exploratory approach included modelling the concentration–time profile of linezolid using a two-compartment model. The model included R(1) to represent the rate of infusion or B for bolus oral input, Ka to represent the rate constant for oral absorption, Vc as the volume of the central compartment, Vp as the volume of the peripheral compartment, CLd as the intercompartment distribution clearance and CL as the total clearance from the central compartment. POP-PK modelling was achieved using maximum-likelihood estimation using the ‘IVOral’ approach by naive pooled data analysis as detailed in the ADAPT 5 user guide.

Alternate models of higher and lower complexity including evaluation of non-linear CL through Michaelis–Menten models were tested. Discrimination between the initial and alternate models was accomplished by the rule of parsimony based on the Akaike information criterion (AIC). An additive and proportional error variance model was used to estimate the relationship between measured concentrations and variance. The additive component was fixed (SD intercept) and the proportional component (SD slope) was fit for the population but served as a fixed effect for individuals. The SD intercept was modified as necessary based on the fit of the model. Covariates of system parameters were evaluated post hoc through a review of scatter plots and regression analysis. Significant covariates were introduced into the model and final model selection was based on the AIC.

POP-PK model validation

Evaluation of the final POP-PK model was performed using diagnostic plots. The diagnostic plots included population and individual predicted versus observed plots, residuals versus time and residuals versus individual predicted concentration. Predictive check of the final POP-PK model was performed via Monte Carlo simulation of 5000 subjects to compare concentration–time and area under the serum concentration–time curve integrated to 12 h (AUC₀₋₁₂) and 24 h (AUC₀₋₂₄) and infinity (AUC₀₋∞). The POP-PK model estimates of AUC₀₋∞ were compared with those derived by non-compartmental analysis using STATA/SE version
11 (Stata Corp., College Station, TX, USA) by the linear trapezoidal method and extrapolation to infinity (AUC$_{0-\infty}$). The AUC$_{0-\infty}$ results from this study were compared with historical values obtained through non-compartmental pharmacokinetic analyses of single-dose oral linezolid (375 mg and 625 mg) in healthy non-obese volunteers (B. Damle, Pfizer Inc., personal communication). These healthy non-obese volunteer ($n=19$) AUC$_{0-\infty}$ data were acquired from a single-dose pharmacokinetic study (PNU-100766 M/1260/0018) originally performed by Pharmacia & Upjohn. The non-obese control group (89.5% male) had a median (range) age of 28 (19–54) years, weight of 76.4 (51.7–90.7) kg and BMI of 24.3 (19.2–27.8) kg/m$^2$.

**Probability of target attainment (PTA)**

After model validation, a standard 600 mg every 12 h oral regimen of linezolid was evaluated by simulating ($n=5000$) the expected AUC$_{0-24}$ and AUC$_{0-\infty}$ in an adult population with a log-normal mean (percentage coefficient of variation) weight of: (i) 81 (30) kg, general adult population$^{20}$; (ii) 76 (13.6) kg, non-obese controls; and (iii) 124 (8.39) kg, obese pre-RYGBS subjects. The AUC$_{0-24}$ was transformed to free AUC$_{0-24}$ ($\text{fAUC}_{0-24}$) by factoring in the range of linezolid protein binding fixed estimates of 0% and 31% based on microdialysis and product label data.$^{12,21}$ Classification and regression tree analysis were performed to identify weight breakpoints (general population weight distribution) associated with an increased relative hazard ratio for not achieving an fAUC$_{0-24}$/$\text{MIC} \geq 100$ (assuming MIC=1 mg/L). In addition, the PTA for an fAUC$_{0-24}$/MIC $\geq 25$, 50 and 100 based on non-obese controls and obese pre-RYGBS weight distributions was determined (MIC=0.0625–32 mg/L). The fAUC$_{0-24}$/MIC targets were selected based on the EUCAST rationale for linezolid clinical breakpoints for S. aureus. Finally, given publication of the wild-type MIC distribution ($n=60528$) for S. aureus (MIC=0.0625–32 mg/L) by EUCAST,$^{22}$ the cumulative fraction of response (CFR) was calculated as:

$$\sum_{i=1}^{n} \text{PTA}_i \times F_i,$$

where $i$ is the MIC category ranked from lowest to highest MIC value of a population of microorganisms, PTA$i$ is the PTA for the $i$th MIC category and $F_i$ is the fraction of the population of microorganisms for the $i$th MIC category.$^{23}$

**Statistical analyses**

Individual POP-PK parameter and AUC$_{0-\infty}$ estimates (including non-compartmental) were compared between the groups (before and after RYGBS by dosing route) using the Wilcoxon signed rank test. Scatter plots, linear and non-linear (power, polynomial, etc.) regression models and graphs were created using STATA/SE version 11.

**Results**

**Subjects and concentration–time profiles**

Five white subjects (four males and one female) with a median (range) age of 50 (47–60) years completed all four phases of the study. Linezolid was well tolerated by all the subjects and no adverse events were noted. At baseline, the median (range) weight was 128.2 (105.9–135.5) kg with a BMI of 42.6 (38.5–58.1) kg/m$^2$. Approximately 3 months after RYGBS, the subjects had a median (range) weight loss of 30.9 (22.7–43.2) kg. This equated to a post-RYGBS median (range) weight of 92.3 (83.2–98.6) kg and a BMI of 30.9 (28.7–44.6) kg/m$^2$.

The concentration–time profile of linezolid (Figure 1) for each subject clearly demonstrates higher concentrations post-RYGBS.

*Figure 1. Profile of serum concentration over time of iv and oral linezolid following a single 600 mg dose by subject before and after RYGBS.*
compared with pre-RYGBS. The mean (SD) $C_{\text{max}}$ of iv linezolid was 7.33 (1.06) mg/L pre-RYGBS and 9.24 (1.99) mg/L post-RYGBS. The mean (SD) $C_{\text{max}}$ of oral linezolid was 6.74 (2.75) mg/L pre-RYGBS and 8.69 (4.22) mg/L post-RYGBS. The time to $C_{\text{max}}$ was highly variable (0.5–4 h), but this value was identical pre-RYGBS compared with post-RYGBS after oral linezolid for each individual subject. The mean (SD) concentration at 12 h ($C_{12}$) was 0.984 (0.527) mg/L and 2.42 (0.416) mg/L pre-RYGBS and post-RYGBS, respectively, with iv linezolid. The mean (SD) concentration at 12 h ($C_{12}$) was 0.737 (0.815) mg/L and 3.00 (0.720) mg/L pre-RYGBS and post-RYGBS, respectively, with oral linezolid.

**POP-PK**

The population and individual model predicted concentrations versus observed concentrations are provided in Figure 2. The initial structural model provided an excellent fit to the individual model predicted data ($R^2 = 0.95$), but a poor fit to the population model predicted data ($R^2 = 0.43$). The inclusion of total body weight (TBW) as a covariate of CL improved the population model predicted data fit ($R^2 = 0.85$) to the observed data (Figure 2b versus a), with specific details provided below. Alternate models did not further reduce the AIC. The naive pooled data assessment by subject pre-RYGBS and post-RYGBS yielded a mean (95% CI) $F$ of 1.143 (0.8162–1.470) and 1.137 (1.009–1.264), respectively. The initial mean POP-PK system parameter estimates were 9.98 L/h (CL), 61.5 L (Vc), 2.14 h$^{-1}$ (Ka), 14.4 L/h (Cl_d) and 18.0 L (Vp). The linezolid CL was significantly correlated ($P<0.001$, $R^2 = 0.58$) to TBW. As shown by the scatter-plot with linear fit (Figure 3), the slope of CL to TBW was similar with iv and oral linezolid. More importantly, a reduction in CL with TBW was evident in all subjects. A significant relationship ($P<0.05$) between CL and lean body weight (LBW) was also observed, but the $R^2$ values were 0.31 and 0.38 for the oral

**Figure 2.** Scatter and linear fit plot of the population model predicted (Ppred) concentrations without TBW (a) and with TBW (b) as a covariate of clearance and individual model predicted (Ipred) concentrations without TBW (c) and with TBW (d) as a covariate of clearance versus observed serum concentrations (Obs).
and iv data. No significant relationships between TBW or LBW and other POP-PK system parameter estimates (Vc, Vp and CLd) were observed. So TBW was introduced as a covariate of CL in the POP-PK model and tested as linear, polynomial and power (TBWb) functions. The relationship of CL to TBW was best described by:

\[ CL(L/h) = 0.214 \times TBW - 12.6. \]

Table 1 includes the POP-PK system parameter estimates, including the individual estimates before and after RYGBS. As shown, TBW and CL were significantly lower post-RYGBS compared with pre-RYGBS values. The mean AUC0–1 values were 86.4% higher post-RYGBS compared with values pre-RYGBS. For comparison, the mean (% coefficient of variation) AUC0–1 values based on non-compartmental analysis pre-RYGBS and post-RYGBS were 42.6 (31.1) mg·h/L and 88.4 (26.5) mg·h/L, respectively. The AUC0–1 values post-RYGBS were on average more than 50% lower than the values post-RYGBS and data from non-obese controls administered a single oral dose of 625 mg linezolid (Figure 4). The single-dose AUC0–1 values pre-RYGBS in obese subjects (600 mg) were also lower than those observed after a single oral dose of 375 mg in non-obese controls (Figure 4).

**PTA**

The relative hazard ratio (RHR) was 2.61 for not achieving an fAUC0–24 ≥100 in individuals ≥90 kg compared with <90 kg in the simulated general adult population weight distribution and assumption of 31% protein binding. With the assumption of 0% protein binding, the RHR was 7.22 for not achieving the same target in individuals ≥108 kg compared with <108 kg. These differences in the risk of not achieving the fAUC0–24/MIC in obese compared with non-obese adult weight population simulations are also evident in Table 2. As tabulated, the PTA (fAUC0–24/MIC ≥100) was <90% for MIC values ≥1 mg/L (non-obese) and >0.25 mg/L (obese) in simulations of weight distributions that mimic our control and study groups.

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**Table 1.** POP-PK system parameter estimates based on the population model and individual model outputs before and after RYGBS, including AUC estimates based on simulation with TBW distributions for each corresponding group

<table>
<thead>
<tr>
<th>System parameter</th>
<th>Population model</th>
<th>pre-RYGBS</th>
<th>post-RYGBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBW (kg)</td>
<td>108 (3.77)</td>
<td>124 (8.51)</td>
<td>92.4 (6.15)</td>
</tr>
<tr>
<td>Ka (h⁻¹)</td>
<td>1.64 (25.2)</td>
<td>2.46 (88.1)</td>
<td>3.54 (119)</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>9.98 (10.2)</td>
<td>15.5 (31.2)</td>
<td>9.97 (13.9)</td>
</tr>
<tr>
<td>Vc (L)</td>
<td>61.6 (5.26)</td>
<td>65.3 (17.5)</td>
<td>62.0 (21.8)</td>
</tr>
<tr>
<td>Vp (L)</td>
<td>18.2 (21.1)</td>
<td>30.7 (57.4)</td>
<td>25.1 (56.8)</td>
</tr>
<tr>
<td>CLd (L/h)</td>
<td>6.80 (29.0)</td>
<td>14.3 (124)</td>
<td>17.9 (111)</td>
</tr>
</tbody>
</table>

Simulation (n=5000)

| AUC0–12 (mg·h/L) | 44.5 (11.3) | 36.9 (9.48) | 53.5 (13.5) |
| AUC0–24 (mg·h/L) | 54.2 (9.98) | 42.2 (8.89) | 70.7 (11.7) |
| AUC0–∞ (mg·h/L) | 57.9 (11.0) | 43.5 (9.49) | 81.1 (13.6) |

System parameters: Ka, rate constant for oral absorption; CL, total clearance; Vc, volume of the central compartment; Vp, volume of the peripheral compartment; CLd, intercompartment distribution clearance.

Reported as mean (% relative standard error).

Reported as mean (% coefficient of variation), with the simulation of a single 600 mg oral dose of linezolid using the population system parameter estimates and CL = 0.214 × TBW – 12.6.

P<0.001, comparing post-RYGBS with pre-RYGBS.
respectively. The predicted CFR was 31.6%–70.9% in the non-obese population compared with 2.51%–28.9% in the obese population simulations across the three \( fAUC_{0-\infty}/MIC \) targets. For comparison, the EUCAST-predicted CFR with the same linezolid dose simulation (non-inclusion of weight, 31% protein binding) was \( \geq 86.2\% \) (data not shown).

### Discussion

The current quantitative analysis provides important information about the influence of body size and RYGBS on the pharmacokinetics of linezolid. We observed no alteration in the oral bioavailability of linezolid after RYGBS, but demonstrated a clear relationship between linezolid \( CL \) and TBW. These results have important implications for the design of future studies that seek to further quantify the exposure–response relationship of linezolid in obese individuals. As also observed by other groups, the systemic exposure profile of linezolid was markedly lower in obese compared with unmatched non-obese controls. However, the unique design of our study permitted the evaluation of the relationship of linezolid \( CL \) to TBW in the same individual. All five obese subjects demonstrated a clear reduction in linezolid \( CL \) with weight loss post-RYGBS. This finding is significant because previous POP-PK models suggested a potential relationship between linezolid \( CL \) and body size.\(^{16,17}\) However, they could not confirm independence of body size as a covariate due to population heterogeneity, inclusion of sparse concentration–time data per subject and no repeated measurements.\(^{16,17}\) If linezolid \( CL \) increases with TBW, then the AUC will decrease with body weight if the dose is not adjusted: \( AUC_{0-\infty} = \text{dose}/CL \). Validation of this finding in future studies has clear implications to our current use of a fixed dose of linezolid without regard to body weight. Herein we provide implications and limitations of our data based on available information.

To date, two formal POP-PK analyses have been performed with inclusion of very different datasets.\(^{16,17}\) Meagher et al.\(^{16}\) utilized sparse concentration–time data from 318 subjects enrolled in a linezolid compassionate use programme. This important investigation included subjects (52.2% male) across a wide range of ages (14–88 years) and weights (37–200 kg).

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**Table 2.** Percentage PTA and CFR in non-obese and obese weight distributions across a EUCAST-published MIC distribution for \( S. \text{aureus}^{22} \)

<table>
<thead>
<tr>
<th>MIC (mg/L)</th>
<th>n</th>
<th>25</th>
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<tr>
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<td>1464</td>
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<td>2</td>
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<td>8</td>
<td>28</td>
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<tr>
<td>CFR (%)</td>
<td>99.3</td>
<td>70.9</td>
<td>31.6</td>
<td>83.6</td>
<td>28.9</td>
<td>2.51</td>
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\( fAUC_{0-\infty} = \text{area under the free (assuming protein binding of 31\%)} \) concentration–time curve integrated from time 0 to infinity.

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**Figure 4.** Box and whisker plot of the non-compartmental estimates of \( AUC_{0-\infty} \) before and after RYGBS compared with non-obese controls after a single oral dose of linezolid.
extensive analysis only TBW and creatinine clearance (Cockcroft–Gault, which includes age, TBW and sex) were identified as covariates of linezolid CL. The mean linezolid average total CL was 6.85 L/h/65 kg, which equates to 13.1 L/h in a 124 kg individual and is comparable to our model estimate (13.9 L/h) for this 124 kg individual. An alternate POP-PK analysis of five Phase 2/3 studies in 455 subjects (58.2% male) also included individuals across a wide range of ages (19–98 years) and weights (30–190.5 kg). This later model identified both age (linear and indicator variable) and weight (power function) as important covariates of linezolid CL. The predicted linezolid CL in a 50-year-old 65 and 124 kg individual by this alternate POP-PK model is 5.85 and 8.54 L/h, respectively. Although these absolute estimates of CL are lower, they do suggest the potential for a 46% lower AUC$_{0\rightarrow\infty}$ in the 124 kg versus the 65 kg individual administered the same dose. Our observation of a reduction in CL after bariatric surgery may have been a consequence of altered renal haemodynamics with weight loss, such as a reduction in glomerular hyperfiltration and proteinuria. However, our study did not measure the renal CL of linezolid to appropriately investigate this parameter as a source of the reduction in total drug CL.

Apart from these formal POP-PK analyses, a small sample of case reports have measured linezolid concentrations in obese subjects. Stein et al. evaluated the serum concentration–time profile of oral linezolid after a variable number (3–12) of doses of 600 mg every 12 h in seven obese subjects with cellulitis. This case series included subjects with a mean (range) weight of 146 (101–195) kg and measurement of three concentrations (one before the pharmacokinetic assessment) considered the 12 h value and two concentrations (1 and 6 h) after the witnessed morning dose of linezolid. Given that a variable number of doses were administered, it is difficult to compare the reported concentrations in these subjects. However, the difference between pre-dose and 1 h post-dose concentrations in their study is a mean (% coefficient of variation) of 8.02 (29.9) mg/L, which is comparable to the C$_{\text{max}}$ values observed in our obese subjects. The uncontrolled nature of the study sampling design and use of the linear trapezoidal rule to calculate AUC$_{0\rightarrow\infty}$ despite variable doses and unverifiable dose administration times limits direct comparison of our data with this previous study. However, it does suggest lower concentrations in obese compared with those expected in non-obese subjects.

In contrast, the well-controlled data after the single dose administration in the healthy non-obese controls of 375 mg followed by 625 mg dose of linezolid in the same individuals permitted better comparisons with our data. The median exposure in our obese pre-RYGBS subjects with a single 600 mg dose was lower than either the 375 mg or 625 mg dose in the non-obese controls. This difference was a function of higher CL in the obese pre-RYGBS group because the exposures were comparable after the 600 mg dose in the post-RYGBS group (due to weight loss) to the 625 mg non-obese control group. The lower exposure in obese adults has also been reported in two independent case reports of a 116 kg male with a pulmonary infection and a 286 kg male with cellulitis.

The lower exposures in obese subjects corresponded to a lower PTA even with the use of lower target values (fAUC$_{0\rightarrow\infty}$/MIC $<$ 100) and a 31% protein binding estimate. An assumption of 0% protein binding (based on microdialysis data) increased the CFR to 52.9% for an fAUC$_{0\rightarrow\infty}$/MIC = 100 in obese individuals, but was still $<$ 90% for lower target values. Despite these predicted (POP-PK models) and observed (case reports) differences in the pharmacokinetic profile and the risk for low PTA among obese subjects, no increased risk in clinical failures has been reported. A pooled analysis of three prospective randomized Phase 3/4 clinical trials of subjects with complicated skin and skin structure infections (cSSTIs) secondary to MRSA and treated with standard doses of linezolid has been performed. This analysis was performed to compare the rate of clinical and microbiological success within four weight quartiles: $<$ 67 kg, $\geq$ 67–78 kg, $\geq$ 79–95 kg and $\geq$ 96–159 kg. Although these results are presently only available as a scientific abstract, they suggest a lack of increased risk of linezolid failure across these weight quartiles. However, given that linezolid may be used for clinical indications beyond cSSTI, risks for underexposure in obese subjects may be detrimental. Specifically, the societal risk for the emergence of linezolid resistance among MRSA isolates should not be ignored. In vitro data have suggested the potential for the emergence of linezolid resistance among MRSA strains exposed to a steady linezolid concentration that mimicked an fAUC$_{0\rightarrow\infty}$/MIC $=$ 24 and the percentage of time above MIC of 100%. Although a range of fAUC$_{0\rightarrow\infty}$/MIC exposures were not evaluated, emergence of resistance was not observed at concentrations that mimicked an fAUC$_{0\rightarrow\infty}$/MIC $=$ 120. This potential risk for emergence of resistance is concerning given the PTA fAUC$_{0\rightarrow\infty}$/MIC $=$ 25 is lower in obese compared with non-obese individuals.

As expected, our study has clear limitations that demand caution when interpreting our data. We studied a single dose of linezolid on four occasions (non-randomized) in a small sample of subjects. Consequently our identification of weight as the only covariate of CL does not exclude the possibility of the existence of other covariates. Furthermore, previous studies have suggested that linezolid may exhibit non-linear pharmacokinetics and could undergo autoinhibition of its CL over time. This potential for non-linear clearance was the primary reason we only simulated the standard two 600 mg every 12 h doses in adults. Finally, our blood sampling scheme was limited during the oral absorption phase (0.5–4 h) and contributed to a marked imprecision in our estimates of Ka and ClD. In spite of these limitations, our single-dose study demonstrated that the oral bioavailability of linezolid is not reduced after RYGBS. This is important because $>$ 200 000 bariatric surgical procedures are performed every year in the USA alone. Our data also demonstrated relationships and trends observed in subjects and previous POP-PK investigations. Taken together, these data clearly demonstrate that the pharmacokinetics of linezolid are altered in obese subjects. Higher doses of linezolid than the current standard are needed in obese subjects to achieve isometric exposures similar to those in non-obese subjects. Future studies should better quantify the linezolid exposure–response (including safety) and exposure–risk of emergence of resistance relationships. This will help to define whether dose modification (e.g. 600 mg every 8 h or 900 mg every 12 h) is necessary in morbidly obese subjects.

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