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PHARMACOLOGY

Pharmacokinetics of Telavancin at Fixed Doses in Normal-Body-Weight and Obese (Classes I, II, and III) Adult Subjects

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ABSTRACT A recommended total-body-weight (TBW) dosing strategy for telavancin may not be optimal in obese patients. The primary objective of this study was to characterize and compare the pharmacokinetics (PK) of telavancin across four body size groups: normal to overweight and obese classes I, II, and III. Healthy adult subjects ($n = 32$) received a single, weight-stratified, fixed dose of 500 mg ($n = 4$), 750 mg ($n = 8$), or 1,000 mg ($n = 20$) of telavancin. Noncompartmental PK analyses revealed that subjects with a body mass index (BMI) of ≥40 kg/m² had a higher volume of distribution (16.24 ± 2.7 liters) than subjects with a BMI of <30 kg/m² (11.71 ± 2.6 liters). The observed area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) ranged from 338.1 to 867.3 mg · h/liter, with the lowest exposures being in subjects who received 500 mg. $AUC_{0-\infty}$ values were similar among obese subjects who received 1,000 mg. A two-compartment population PK model best described the plasma concentration-time profile of telavancin when adjusted body weight (ABW) was included as a predictive covariate. Fixed doses of 750 mg and 1,000 mg had similar target attainment probabilities for efficacy as doses of 10 mg/kg of body weight based on ABW and TBW, respectively. However, the probability of achieving a target area under the concentration-time curve from time zero to 24 h of ≥763 mg · h/liter in association with acute kidney injury was highest (19.7%) with TBW-simulated dosing and lowest (0.4%) at the 750-mg dose. These results suggest that a fixed dose of 750 mg is a safe and effective alternative to telavancin doses based on TBW or ABW for the treatment of obese patients with normal renal function and Staphylococcus *aureus* infections. (This study has been registered at ClinicalTrials.gov under identifier NCT02753855.)

KEYWORDS telavancin, pharmacokinetics, obesity

Telavancin is a semisynthetic lipoglycopeptide antibiotic that has demonstrated potent *in vitro* bactericidal activity against *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), and strains with reduced vancomycin susceptibility, *Enterococcus faecalis*, and *Streptococcus* species (1–3). In 2014, the Clinical and Laboratory Standards Institute approved a revision of the broth microdilution susceptibility test methodology for telavancin, resulting in a more accurate method for determining MIC values (4, 5). The U.S. Food and Drug Administration subsequently revised the MIC interpretive breakpoint criteria for susceptibility to telavancin for *S. aureus* (≤0.12 mg/liter), *Streptococcus pyogenes* (≤0.12 mg/liter), *Streptococcus agalactiae* (≤0.12 mg/liter), members of the *Streptococcus anginosus* group (≤0.06 mg/liter), and *Enterococcus faecalis* (vancomycin susceptible, ≤0.25 mg/liter) (6).

Telavancin is approved for use in the United States for the treatment of complicated skin and skin structure infections and hospital-acquired bacterial

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pneumonia (HABP) or ventilator-associated bacterial pneumonia (VABP) caused by *S. aureus* when alternative treatments are not suitable (6, 7). Clinical studies support its use in the treatment of uncomplicated bacteremia, and an ongoing investigation is evaluating telavancin for the treatment of complicated *S. aureus* bacteremia, including endocarditis (7–10). The dosing of telavancin is based on total body weight (TBW). The approved dosing regimen for patients with normal renal function is 10 mg/kg of body weight by intravenous infusion over 60 min every 24 h, with recommended dose adjustments to 7.5 mg/kg every 24 h for patients with an estimated creatinine clearance (eCL_{CR}) of 30 to 50 ml/min and to 10 mg/kg every 48 h for patients with an eCL_{CR} of 10 to 29 ml/min (6).

The 24-h unbound (free) area under the concentration-time curve (*f*AUC)-to-MIC ratio (*f*AUC/MIC) is considered the best predictor of the antibacterial efficacy of telavancin (11, 12). Most evaluations of pharmacokinetic (PK)-pharmacodynamic (PD) relationships for telavancin have been limited to the total AUC/MIC ratio and were performed with older methods for determining the MIC values (13–16). A recent pharmacodynamic study of telavancin in neutropenic mouse thigh and lung infection models against *S. aureus* used the revised susceptibility testing (11). The mean ± standard deviation (SD) *f*AUC/MIC ratios associated with a 1-log_{10} reduction in the CFU count from stasis were 215 ± 130 and 76.4 ± 49.2, respectively.

Exposure-response relationships for safety are another important pharmacokinetic-pharmacodynamic evaluation. Although telavancin has been well tolerated, nephrotoxicity and worsening renal impairment have occurred during telavancin therapy (17–20). A recent evaluation of safety data from patients enrolled into the clinical trials evaluating the use of telavancin for the treatment of HABP and VABP (ATTAIN) described the relationship between acute kidney injury (defined as a 0.5-mg/dl or 50% increase in the serum creatinine level from the baseline) and telavancin exposure (21). On the basis of classification and regression tree (CART) analysis, a total AUC from time zero to 24 h (AUC_{0-24}) of ≥763 mg · h/liter was associated with a higher rate of acute kidney injury than a total AUC_{0-24} of <763 mg · h/liter. These results are similar to the recent evidence suggesting a maximum AUC_{0-24} limit of 700 mg · h/liter (range, 600 to 800 mg · h/liter) for vancomycin-associated nephrotoxicity (22).

A better understanding of the optimal dosing of telavancin in overweight and obese patients is critical since the prevalence of overweight adults now exceeds 35% of the global population (23). Pharmacokinetic data for telavancin in obese subjects are limited since the median body weight of patients included in previous studies was less than 80 kg (24). Population pharmacokinetic modeling and simulations of the AUC_{0-24} of telavancin have suggested that 10-mg/kg doses based on TBW may not lead to equivalent exposures over a range of total body weight of from 30 to 173 kg (20, 24). In addition, a higher rate of kidney injury after telavancin administration in patients with a body mass index (BMI) of ≥35 kg/m^2 than in those with a BMI of <35 kg/m^2 further suggests the need to investigate the pharmacokinetics-pharmacodynamics of telavancin in the obese population to limit potential dose-related toxicities (25).

The primary objective of this study was to characterize the single-dose pharmacokinetics of telavancin in normal to overweight and obese (classes I, II, and III) healthy adult subjects. Four obesity classifications were chosen as a stratified enrollment scheme (Table 1) to support the determination of relationships between body size and pharmacokinetic parameters (26, 27). Population pharmacokinetic modeling was applied to the observed pharmacokinetic data to investigate exposure-response relationships in obese and nonobese healthy subjects. The secondary objective was to assess the safety and tolerability of telavancin after intravenous administration using clinical evaluation and urinary biomarkers of subclinical kidney injury.

RESULTS

Thirty-two subjects met the criteria for inclusion and received a single intravenous dose of telavancin. The baseline characteristics for the enrolled subjects stratified by obesity class are described in Table 2. As expected, the TBW and BMI increased

TABLE 1 Weight categorization and dosing of telavancin in obese and nonobese adult subjects[a]

Category	BMI (kg/m^2)	TBW (kg)	Telavancin dose (mg)	No. of subjects
Normal-overweight	18.5–29.9	50–74.9	500	4
Normal-overweight	18.5–29.9	75–99.9	750	4
Obese class I	30–34.9	90–99.9	750	4
Obese class I	30–34.9	100–115	1,000	4
Obese class II	35–39.9	105–130	1,000	8
Obese class III	≥40	≥120	1,000	8

[a]Abbreviations: BMI, body mass index; TBW, total body weight.

consistently within each obesity class (Fig. 1). The average values for measured creatinine clearance (mCL_{CR}) were approximately 40% to 79% higher than those for eCL_{CR}.

Noncompartmental pharmacokinetic analysis. Box plots of the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) of telavancin in obese and nonobese subjects are displayed in Fig. 2. The range of $AUC_{0-\infty}$ for all subjects for the three dose levels was 338.1 to 867.3 mg · h/liter, with the median values for each obesity subclass ranging from 497.8 to 602.4 mg · h/liter. Normal to overweight subjects who received a dose of 500 mg had the lowest systemic exposure (mean ± SD $AUC_{0-\infty}$, 441.2 ± 89.9 mg · h/liter). Normal to overweight subjects and obese class I subjects who received a 750-mg dose had similar mean ± SD values of $AUC_{0-\infty}$ (498.6 ± 28.7 versus 504.0 ± 50.4 mg · h/liter, respectively). The mean ± SD values of $AUC_{0-\infty}$ for the three obese classes of subjects who received a single 1,000-mg dose were also similar (598.4 ± 65.0, 618.6 ± 70.3, and 612.4 ± 131.1 mg · h/liter, respectively, for obese classes I, II, and III, respectively). The largest variability (i.e., coefficient of variation, ~21%) in $AUC_{0-\infty}$ was observed at the 500-mg and 1,000-mg doses in normal to overweight and obese class III subjects, respectively.

The observed and calculated noncompartmental pharmacokinetic parameters for each weight class are presented in Table 3. The mean ± SD values for maximum plasma concentrations (C_{max}) in normal to overweight subjects for both the 500-mg and 750-mg doses were similar (66.9 ± 5.7 versus 69.2 ± 6.1 mg/liter, respectively) and were the lowest average C_{max} values among the four weight classes. Obese class I subjects who received the 750-mg and 1,000-mg doses had the highest C_{max} values (mean ± SD, 95.4 ± 29.3 and 88.7 ± 15.2 mg/liter, respectively). The latter C_{max} values tended to be slightly higher than those observed in obese class II and III subjects (Table 3). The volume of distribution at steady state (V_{ss}) tended to increase among the four

TABLE 2 Demographics of obese and nonobese adult subjects[a]

Characteristic	Value for the following subjects:			
	Normal to overweight (n = 8)	Obese class I (n = 8)	Obese class II (n = 8)	Obese class III (n = 8)
Mean ± SD age (yr)	30.8 ± 8.2	29.8 ± 9.0	28.5 ± 6.1	36.3 ± 8.5
No. (%) of male subjects	4 (50)	6 (75)	6 (75)	4 (50)
No. (%) of subjects of the following race/ethnicity:				
Black	2 (25)	3 (37.5)	3 (37.5)	4 (50)
White, Hispanic	1 (12.5)	2 (25)	2 (25)	1 (12.5)
White, non-Hispanic	3 (37.5)	2 (25)	2 (25)	1 (12.5)
Other	2 (25)	1 (12.5)	1 (12.5)	2 (25)
Mean ± SD total body wt (kg)	72.2 ± 12.2	102.4 ± 8.9	110.0 ± 5.9	140.2 ± 9.8
Mean ± SD adjusted body wt (kg)	67.9 ± 7.6	82.9 ± 7.9	84.3 ± 6.2	96.6 ± 5.6
Mean ± SD ht (in.)	67.6 ± 1.8	68.9 ± 2.8	67.9 ± 2.4	68.2 ± 1.6
Mean ± SD BMI (kg/m^2)	24.4 ± 3.3	33.2 ± 1.4	36.8 ± 1.4	46.2 ± 2.5
Mean ± SD eCL_{CR} (ml/min)	91.5 ± 20.5	98.2 ± 18.2	97.7 ± 14.7	90.5 ± 7.9
Mean ± SD mCL_{CR} (ml/min)	127.5 ± 16.2	175.9 ± 37.3	165.2 ± 36.0	151.1. ± 28.2

[a]Abbreviations: BMI, body mass index; eCL_{CR}, estimated creatinine clearance calculated using the Cockcroft-Gault equation (42) and ideal body weight (40); mCL_{CR}, measured creatinine clearance determined from a 24-h urine creatinine collection.

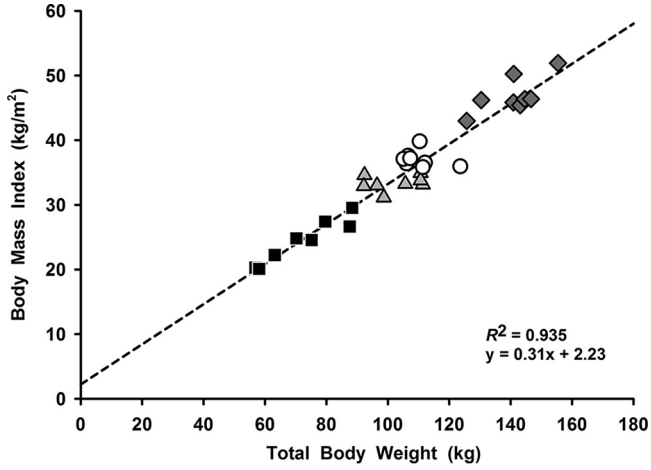

FIG 1 Total body weight versus body mass index of the enrolled obese and nonobese subjects. The dashed line represents the linear regression fit. Symbols represent subjects enrolled into one of four body size groups: normal to overweight (black squares), obese class I (gray triangles), obese class II (open circles), and obese class III (gray diamonds).

weight classes, and subjects with a BMI of ≥40 kg/m² had a significantly higher V_{ss} (16.24 ± 2.7 liters) than subjects with a BMI of <30 to 34.9 kg/m² (13.04 ± 1.5 liters) and <30 kg/m² (11.71 ± 2.6 liters). No significant differences in total body clearance (CL), renal clearance (CL_R), and elimination half-life ($t_{1/2}$) were observed among the groups. The 24-h recovery of telavancin in the urine represented 67.5% ± 7.1% of the administered dose.

Population pharmacokinetic modeling. Population pharmacokinetic analysis was performed with 414 plasma samples from 32 study subjects. A two-compartment linear model provided an improved fit over a one-compartment model (Table 4). Consistent with the noncompartmental analyses, no significant relationships between CL and body size parameters or CL_{CR} were retained in the population model. The lack of a relationship with CL_{CR} in this study is most likely due to the recruitment of healthy subjects with eCL_{CR} values of ≥60 ml/min and the minimal differences in renal function between the stratified classes (Table 2). These analyses included allometric and linear functions of body size. The final model included the volume of distribution in the

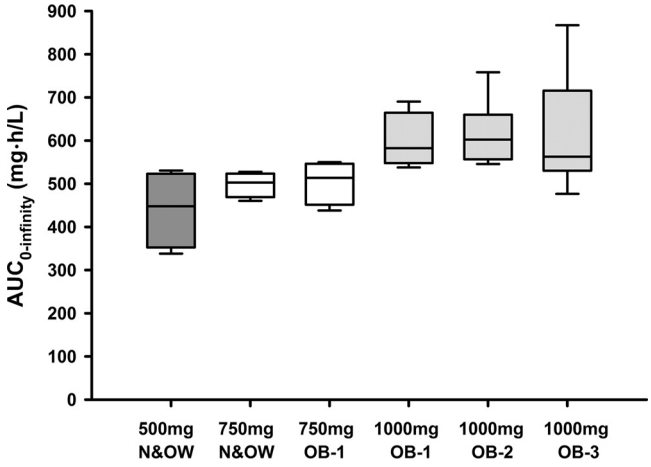

FIG 2 Box plot of the area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) of telavancin in obese and nonobese subjects after a single weight-stratified fixed dose of 500 mg, 750 mg, or 1,000 mg. The ends of the boxes define the 25th and 75th percentiles, with the line at the median and the error bars defining the 10th and 90th percentiles, respectively. Abbreviations: N&OW, normal and overweight; OB-1, obese class I; OB-2, obese class II; OB-3, obese class III.

TABLE 3 Noncompartmental PK parameters of telavancin in obese and nonobese adult subjects[a]

Subgroup	C_{max} (mg/liter)	$AUC_{0-\infty}$ (mg · h/liter)	CL (liters/h)	CL_R (liters/h)	V_{ss} (liters)	$t_{1/2}$ (h)
Normal to overweight ($n = 8$)	68.0 ± 5.6[A]	469.9 ± 69.0[B,C]	1.34 ± 0.25	0.99 ± 0.17	11.71 ± 2.6[B,C]	6.10 ± 0.6
Obese class I ($n = 8$)	92.0 ± 21.9[A]	551.2 ± 73.8	1.59 ± 0.18	1.19 ± 0.13	13.04 ± 1.5[D]	5.82 ± 0.5
Obese class II ($n = 8$)	86.7 ± 9.6	618.6 ± 70.3[B]	1.63 ± 0.17	1.25 ± 0.15	15.06 ± 2.2[B]	6.38 ± 0.8
Obese class III ($n = 8$)	79.8 ± 13.2	612.4 ± 131.1[C]	1.69 ± 0.31	1.10 ± 0.22	16.24 ± 2.7[C,D]	6.68 ± 0.9

[a]Statistically significant differences ($P < 0.05$) between subgroups are indicated as follows: A, normal to overweight compared to obese class I; B, normal to overweight compared to obese class II; C, normal to overweight compared to obese class III; D, obese class I compared to obese class III. Abbreviations: C_{max}, maximum plasma concentration; $AUC_{0-\infty}$, area under the concentration-time curve from time zero to infinity; CL, total body clearance; CL_R, renal clearance; V_{ss}, volume of distribution at steady state; $t_{1/2}$, elimination half-life.

central compartment (V_c), the volume of distribution in the peripheral compartment (V_p), and the intercompartmental clearance (Q) term as a linear function (slope only) of adjusted body weight (ABW). Total body clearance was a noncovariate structured parameter. The median parameter estimates for V_c, V_p, Q, and CL were 0.079 liter/kg, 0.089 liter/kg, 0.080 liter/h · kg, and 1.579 liters/h, respectively. The pharmacokinetic parameter estimates for the two base and final PK models, along with the marked reduction in the Akaike information criterion (AIC) and the improvement in the population model fit, are shown in Table 4. Figure 3 illustrates the excellent observed versus population model predicted and observed versus individual predicted fits ($R^2 = 0.941$ and 0.992, respectively). The final visual predictive check (VPC) is provided as an internal validation of the final model (Fig. 4).

Monte Carlo simulation. The median values for AUC_{0-24} for the single 500-mg, 750-mg, and 1,000-mg doses were 291 mg · h/liter (5th and 95th percentiles, 221 and 402 mg · h/liter, respectively), 436 mg · h/liter (5th and 95th percentiles, 339 and 610 mg · h/liter, respectively), and 583 mg · h/liter (5th and 95th percentiles, 442 and 803 mg · h/liter, respectively), respectively. In contrast, the median values for AUC_{0-24} for a single 10-mg/kg dose based on TBW and ABW were 617 mg · h/liter (5th and 95th percentiles, 328 and 976 mg · h/liter, respectively) and 483 mg · h/liter (5th and 95th percentiles, 325 and 694 mg · h/liter, respectively), respectively. When comparing the 95th and 5th percentile values, fixed doses were up to 1.82-fold different, while TBW-based dosing generated a range that was approximately 3-fold different.

The target attainment rate for the 24-h *f*AUC/MIC ratio breakpoint of 76.4 was 100% for all dosage regimens (fixed and weight based) of telavancin when MIC values were 0.25 mg/liter or less. When the breakpoint of 215 was evaluated, the 750- and 1,000-mg fixed-dose regimens achieved a target attainment rate of 100% when MIC values were 0.125 mg/liter or less. A dose of 10 mg/kg based on ABW and TBW resulted in nearly identical target attainment rates (99.9% and 99.8%, respectively) for MIC values of 0.125 mg/liter or less. Only doses of 1,000 mg and 10 mg/kg based on TBW resulted in target attainment rates of >90% when MIC values were 0.5 mg/liter and 0.25 mg/liter for 24-h *f*AUC/MIC ratios of 76.4 and 215, respectively.

The larger range of AUC values with TBW-based dosing impacted the probability for exposures associated with acute kidney injury. The probability of a total AUC_{0-24} of ≥763 mg · h/liter was 19.7% for a dose of 10 mg/kg based on TBW, whereas it was 7.9% for a dose of 1,000 mg. The probabilities of a total AUC of ≥763 mg · h/liter were only 0.4% and 0.8% for doses of 750 mg and 10 mg/kg based on ABW, respectively.

TABLE 4 Representative and final covariate structured population PK model for telavancin in obese and nonobese adult subjects[a]

Model	V_c (liters)	CL (liters/h)	V_p (liters)	Q (liters/h)	AIC	R^2
One compartment	12.9 ± 2.48	1.58 ± 0.247	NA	NA	2,478	0.806
Two compartment	6.70 ± 1.57	1.57 ± 0.255	7.53 ± 1.75	7.24 ± 2.18	2,012	0.882
Two compartment[b]	6.40 ± 1.10	1.57 ± 0.252	7.20 ± 1.35	6.88 ± 1.18	1,957	0.941

[a]Values are reported as means ± standard deviations. Abbreviations: V_c, volume of distribution in the central compartment; CL, total body clearance; V_p, volume of distribution in the peripheral compartment; Q, intercompartmental clearance; AIC, Akaike information criterion; R^2, coefficient of determination for the observed versus population predicted values.

[b]Final covariate structured model for V_c, V_p, and Q as a linear function of adjusted body weight with values scaled to an 80-kg individual.

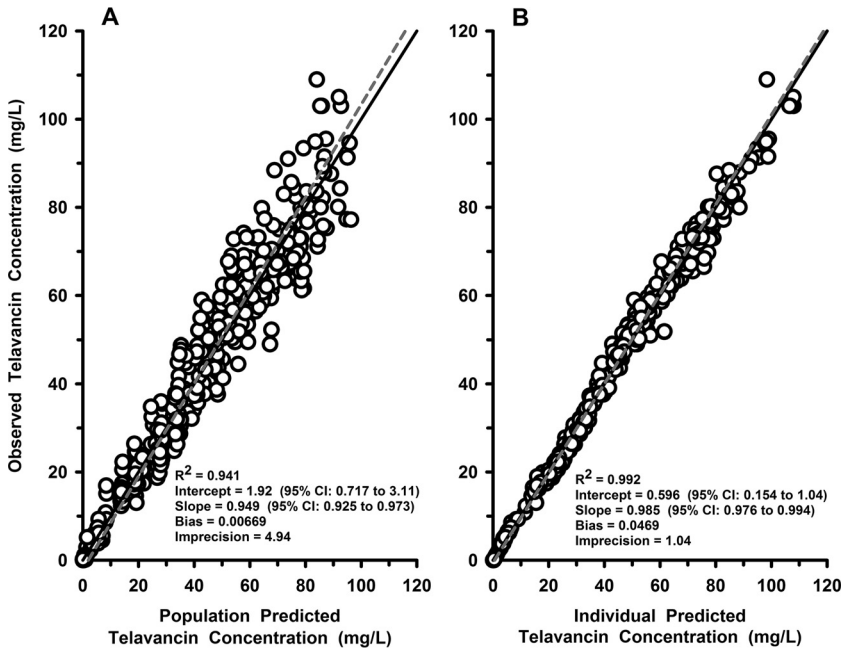

FIG 3 Goodness-of-fit plots for the final two-compartment pharmacokinetic model with first-order elimination. (A) Observed versus population predicted telavancin concentrations; (B) observed versus individual predicted concentrations. The lines in each plot represent the lines of identity (solid black lines) and the linear regression lines (gray dashed lines). CI, confidence interval.

Safety and tolerability. A single dose of telavancin was associated with only mild adverse effects in this cohort of healthy subjects. Eighteen (56%) subjects had at least one reported adverse effect, with the majority being mild, transient dysgeusia (14/18, 78%). Other reported adverse effects included nausea ($n = 3$), dry mouth ($n = 2$), loss of appetite ($n = 2$), fatigue ($n = 2$), erythema around the intravenous infusion site ($n = 2$), and headache ($n = 1$). No serious or unexpected adverse effects were observed.

Subclinical kidney injury biomarkers. No statistically significant differences between the 24-h and 48-h values normalized to the baseline values for the 13 tested urinary biomarkers for subclinical kidney injury were observed between groups classified by BMI. No relationships to the $AUC_{0-\infty}$ or C_{max} values of telavancin could be discerned through the review of scatter plots of these biomarkers.

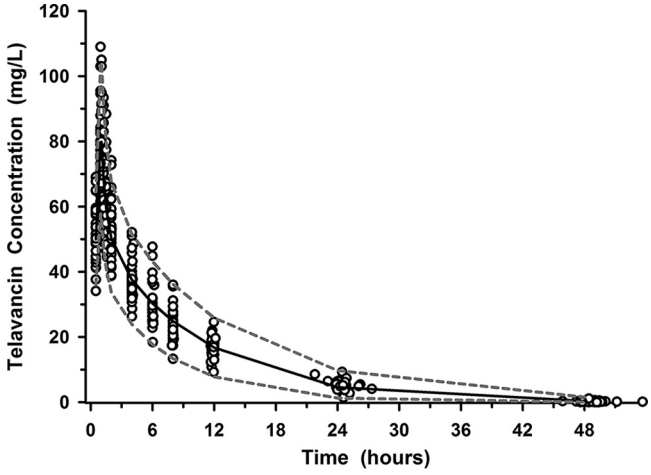

FIG 4 Visual predictive check (VPC) plot displaying the observed telavancin concentrations (open circles) and the 5th (bottom dashed line), 50th (solid line), and 95th (top dashed line) percentile telavancin plasma concentrations versus time simulated from the final covariate model.

DISCUSSION

Dosing of antibacterial agents based on total body weight is a common paradigm that may not be optimal for agents such as telavancin (28). The findings from this pharmacokinetic study clearly highlight an opportunity to consider a fixed dosing strategy for telavancin and/or a maximum dose in obese patients. We observed a higher V_{ss} in healthy subjects with class III obesity (BMI $\geq$ 40 kg/m^2) than in normal to overweight subjects (BMI $<$ 30 kg/m^2). The observed V_{ss} was approximately 40% higher in the class III obese subjects, despite an almost 2-fold difference in total body weight (mean, 140.2 versus 72.2 kg). The increased V_{ss} resulted in the lower C_{max} values observed in the class II and III obese subjects receiving 1,000 mg of telavancin (Table 3).

The total body clearance of telavancin was not significantly different across the classes of obese subjects, and the interindividual variability (i.e., coefficient of variation) was $<$20% (Table 3). The rates of recovery of telavancin in the urine and CL_R were not different among the subjects in the four weight classes, implying no physiological mechanism for enhanced elimination. As a consequence, administration of a weight-stratified, fixed dose of telavancin led to similar $AUC_{0-\infty}$ values in subjects with class I, II, and III obesity. The mean $\pm$ SD $AUC_{0-\infty}$ value of telavancin at 10 mg/kg in previously reported single-dose pharmacokinetic studies was 747 $\pm$ 129 mg · h/liter (7, 29, 30). Our observed range of $AUC_{0-\infty}$ values in obese class II and III subjects (476.7 to 867.4 mg · h/liter) was similar to the values previously reported in nonobese healthy subjects (29–32). The lower $AUC_{0-\infty}$ values observed in our normal-weight subjects can be explained in part by the use of an absolute dose (500 mg in this study) lower than the dose of 10 mg/kg based on TBW in healthy subjects weighing between 60 and 90 kg used in previously reported pharmacokinetic studies.

Population pharmacokinetic analysis of our plasma concentration-time data for telavancin demonstrated that the observed versus individual predicted concentrations were best fitted by a two-compartment model with linear elimination. The inclusion of ABW as a covariate significantly improved the fit of the population model and suggested that TBW may not be a necessary scalar for determination of the telavancin dose in obese subjects. The observed PK parameters and Monte Carlo simulations for fixed doses of 750 mg and 1,000 mg were able to attain the same PK-PD targets of efficacy (e.g., *f*AUC/MIC values) as 10-mg/kg doses based on ABW and TBW, respectively.

An exposure-response relationship has been established for the probability of acute kidney injury with telavancin (21, 33). There was a 1.5 to 1.8 times higher risk of experiencing on-treatment kidney injury among patients who had a total AUC_{0-24} of $\geq$763 mg · h/liter than among those with a lower exposure (21). The analysis also determined that clinical failure and mortality at test of cure were more common when the AUC_{0-24} exceeded this threshold (21). In our analysis, it is clear that TBW-based dosing has the potential to lead to exposures exceeding this value more often than other dosing strategies in obese subjects. In contrast, use of a 750-mg daily dose achieves a high probability of target attainment (PTA) for efficacy with an approximately 50-fold lower probability of exceeding the toxicity target in the tested population. Our results also indicate that doses of up to 1,000 mg have a $<$8% probability of exceeding the toxicity threshold. Use of ABW-based dosing is also associated with a lower probability of toxicity. However, telavancin is presently formulated in 750-mg vials for intravenous infusion. Thus, the practical value of administering a 750-mg dose of telavancin regardless of body weight is self-evident.

Overall, telavancin was well tolerated in our healthy subjects, with only mild adverse effects, such as dysgeusia, being noted. However, serious adverse effects, such as acute kidney injury, have been noted in patients receiving telavancin, particularly in patients with comorbid conditions, such as preexisting kidney disease and diabetes (6). In order to assess potential pharmacokinetic-toxicodynamic relationships between telavancin exposure and kidney injury, we assessed several markers of kidney injury. Other glycopeptides, most notably, vancomycin, have been associated with kidney injury

affecting the proximal tubule (34–37). As such, biomarkers such as KIM-1 and cystatin C, which are more specific to injury affecting the proximal tubule, appear to be the most appropriate markers (35, 36). Markers of overall damage, such as clusterin and osteoponin, have also been reported to have dose-related relationships with vancomycin exposure in rat models (35, 37). Our results suggest that these biomarkers are likely insensitive to subclinical kidney injury after a single fixed dose of telavancin in healthy subjects.

The limitations of this work should be appreciated prior to broad implementation of this alternate dosing paradigm. Protein binding and the unbound fraction were not assessed in this study. The protein binding of telavancin is variable in published studies, so a more conservative estimate of 90% was chosen for PTA analyses (6). However, microdialysis studies in healthy subjects suggest that the unbound fraction may be higher, with a reported range of 0.132 to 0.248 (31). Use of these higher unbound fraction estimates would have led to computation of higher PTA values at lower doses, such as the 500-mg fixed dose. The predictive pharmacodynamic targets used in our analysis (e.g., *f*AUC/MIC values of 76.4 and 215) were linked with a 1-log reduction in the number of CFU from that at the baseline for *S. aureus* in neutropenic murine models (11). Use of this predictive index resulted in telavancin doses that were approximately 2- and 3-fold higher than those obtained when a static endpoint was used in the same animal models (11). Despite the controversy over which pharmacodynamic target (e.g., static versus 1-log kill) is most appropriate to treat a specific infection type, our predictive dosage simulations based on 1-log-kill targets are likely most supportive for treating serious *S. aureus* infections, including bacteremia. In addition, significant variability in the pharmacodynamic targets exists among different Gram-positive bacterial species, so our Monte Carlo simulations are most applicable to *S. aureus* (33). Creatinine clearance and other measures of CL_R were not significant covariates in our population model because all included subjects had normal renal function; thus, our simulation data are specific for patients without renal impairment. In addition, the design used subject self-collection of 12- to 24-h urine samples, which may have resulted in underestimation of the urinary recovery of telavancin and CL_R. Finally, this evaluation was limited by age and weight among the subjects enrolled in this study, which included an upper end of 50 years for age and a modest 154 kg for weight. Extrapolation of these results to subjects with a significantly older age or higher TBW is not advised. The major limitation of the simulation, as noted, is uncertainty related to the optimal pharmacodynamic target and the translatability to clinical outcomes. These limitations do not dampen our clear demonstration that TBW-based dosing of telavancin is not necessary in obese patients.

In summary, the V_{ss} of telavancin was the only pharmacokinetic parameter that tended to increase with body weight, with the highest value being observed in obese class III subjects compared to nonobese and obese class I subjects. Total body clearance and CL_R were not related to body size. Pharmacokinetic modeling and Monte Carlo simulations predicted that a fixed dose of 750 mg administered as an intravenous infusion over 60 min every 24 h achieves a PTA associated with clinical effectiveness similar to that for the current TBW-based dosing recommendation and a probability of toxicity lower than that of the current TBW-based dosing recommendation. If higher systemic exposure in plasma concentrations is desired in obese subjects, our predictions would suggest a maximum fixed dose of 1,000 mg or a dose (i.e., 10 mg/kg) based on ABW. Prospective evaluations of these dosing strategies in a demographically diverse patient population with a wide range of TBW and renal function are needed.

MATERIALS AND METHODS

Study design. This was a phase I, open-label, single-dose pharmacokinetic study in 32 healthy adult subjects. The study protocol was approved by the University of Illinois at Chicago Institutional Review Board, and written informed consent was obtained from each subject prior to enrollment. All study procedures were performed at the Clinical Research Center of the University of Illinois at Chicago Center for Clinical and Translational Science (Chicago, IL). The study was registered with ClinicalTrials.gov (identifier NCT02753855).

Subjects were evenly enrolled into one of four body size groups on the basis of their BMI and TBW: normal to overweight (BMI, 18.5 to 29.9 kg/m^2; TBW, 50 to 99.9 kg), obese class I (BMI, 30 to 34.9 kg/m^2; TBW, 90 to 115 kg), obese class II (BMI, 35 to 39.9 kg/m^2; TBW, 105 to 130 kg), and obese class III (BMI, ≥40 kg/m^2; TBW, ≥120 kg). Both BMI and TBW were required to be within these defined ranges to avoid potential height-related misclassification of obesity and to ensure that the protocol-specified dose did not exceed the 10-mg/kg TBW-based dosing recommendation in the product package information (6). The categorization of obese classes I through III was based on BMI definitions from the Centers for Disease Control and Prevention (38). To enhance the evaluation of any relationship between body size and pharmacokinetic parameters of telavancin, subjects in the normal to overweight class and obese class I were matched to subjects in obese classes II and III based on age (±10 years), sex, and serum creatinine concentration (±0.25 mg/dl)

All subjects received a protocol-defined fixed dose of telavancin (Table 1) by intravenous infusion over 60 min through a peripheral intravenous catheter using a controlled infusion pump. Telavancin hydrochloride (Vibativ) was supplied by Theravance Biopharma R&D, Inc., and reconstituted and diluted according to the manufacturer's recommendations (6).

Study population. Healthy men and women between 18 and 50 years of age were eligible to participate in the study. Potential subjects underwent a screening that included a complete medical history; physical examination; assessment of height, weight, and vital signs; and evaluation of clinical laboratory data. Subjects with clinically significant abnormalities identified on screening were excluded from the study. Females of childbearing potential were required to have a negative serum pregnancy test at screening and within 24 h of telavancin infusion and were required to use acceptable forms of contraception if nonabstinent.

Subjects were excluded from participation if any of the following criteria were met: (i) a history of a significant hypersensitivity reaction or intolerance to telavancin or lipo- or glycopeptide antibiotics; (ii) a history of significant cardiac, neurological, thyroid, muscular, or immune disorders; (iii) a positive serum pregnancy test or current breast-feeding; (iv) a history of alcohol or substance abuse or dependence (including tobacco) within 12 months of study enrollment; (v) a history of prescription or nonprescription drug use if, in the opinion of the investigators, the drug would potentially affect the pharmacokinetics or safety profile of telavancin; (vi) aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels >1.5 times the upper limit of normal; (vii) a serum creatinine concentration of ≥1.5 mg/dl or an eCL_{CR} of <60 ml/min, as determined by the Cockcroft-Gault equation (42) using ideal body weight (IBW) (40), based on the product package information (6); (viii) participation in a clinical trial within the previous 30 days; or (ix) donation of blood within the previous 56 days that resulted in an excess of 500 ml donated. Subject enrollment continued until an appropriate number of matched subjects had been enrolled into each weight classification group (Table 1).

Sample collection. Blood samples for plasma telavancin concentration determination were collected from a peripheral intravenous catheter in the arm contralateral to the arm with the intravenous catheter used for telavancin infusion. Samples were collected prior to infusion (time zero) and at 0.5, 0.95, 1.05, 1.25, 1.5, 2, 4, 6, 8, 12, 24, and 48 h after the start of the infusion. Samples were collected in prechilled 6-ml K_2EDTA-containing tubes and immediately centrifuged under refrigeration at 4°C at 1,500 × *g* for 15 min. The supernatant plasma was collected and stored at −80°C until shipping for sample analysis.

A spontaneously voided spot urine sample for telavancin and biomarker concentration determination was collected prior to telavancin infusion (time zero) and at 24 and 48 h postinfusion. All voided urine was collected for 24 h from the start of telavancin infusion in the time intervals 0 to 6 h, 6 to 12 h, and 12 to 24 h and stored under refrigeration at 4°C until the volume was combined for 24-h measured creatinine clearance (mCL_{CR}) determination. A 5% solution of the zwitterionic detergent 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS; G-Biosciences, St. Louis, MO) was added to urine at the time of each void in a 1:10 volumetric ratio to minimize telavancin binding to the containers used for measurement and storage. Aliquots from each time point were stored at −80°C until shipping for sample analysis.

Analytical procedures. The concentrations of telavancin in plasma and urine were determined by a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay performed at Q2 Solutions (Ithaca, NY). Human plasma collected in K_2EDTA-containing tubes was treated with 0.5% hydroxypropyl-beta-cyclodextrin (H-β-CD); urine contained 0.5% CHAPS solution as described above. Both methods employed a solid-phase extraction technique, followed by a gradient high-performance liquid chromatography method, and a Sciex API-5000 mass spectrometer in positive ionization mode was used. The lower limit of quantification (LLOQ) for the plasma assay was 100 ng/ml, and the calibration curve was linear through the range of 100 to 50,000 ng/ml. The precision (i.e., percent coefficient of variation) and accuracy (i.e., percent bias) of the plasma calibration standards were 3.2 to 4.6% and −4.0 to 1.1%, respectively. The LLOQ for the urine assay was 250 ng/ml, with a range of 250 to 130,000 ng/ml. The precision and accuracy of the urine calibration standards were 3.3 to 10.0% and −2.8 to 6.0%, respectively.

Noncompartmental pharmacokinetic analysis. Individual plasma telavancin concentration-time data were used to calculate the values for the pharmacokinetic parameters using noncompartmental analysis with Phoenix WinNonlin (version 6.4) software (Certara Corp., Princeton, NJ). The maximum plasma concentration (C_{max}) was read from the observed plasma concentration-time profile of telavancin. The area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) and the area under the concentration-time curve from time zero to 24 h (AUC_{0-24}) were estimated with the linear-log trapezoidal method. The terminal elimination rate constant was determined for each subject by linear regression of the terminal portion of the log-linear concentration-time data with a user-defined number of points for

the best-fit line. Calculated pharmacokinetic parameters included the volume of distribution at steady state (V_{ss}), total body clearance (CL), and elimination half-life ($t_{1/2}$). Renal clearance (CL_R) was determined from the cumulative amount of telavancin recovered in urine over 24 h relative to the corresponding AUC_{0-24} in plasma. Plasma concentrations below the LLOQ were treated as zero prior to C_{max} and censored thereafter.

Population pharmacokinetic analysis. Population pharmacokinetic modeling was performed with a nonparametric adaptive grid (NPAG) algorithm in the Pmetrics package for R (Laboratory of Applied Pharmacokinetics, Los Angeles, CA) (39). A one-compartment model and a two-compartment structural model were evaluated, and the model with the best fit was used in subsequent covariate analyses. Clearance (CL) from the central compartment and the intercompartmental clearance (*Q*) were considered to be first-order processes. Concentrations below the LLOQ were treated as zero. A multiplicative assay variance model with a second-degree polynomial fit to the plot of the interday assay standard deviation was used. Covariates with biological plausibility to impact telavancin pharmacokinetics, including age, height, TBW, ideal body weight (IBW) (40), adjusted body weight {ABW; where ABW = IBW + [0.4 × (TBW – IBW)]} (27, 28), lean body weight (41), BMI (38), and the 24-h mCL_{CR} and eCL_{CR} calculated with the Cockcroft-Gault equation (42), were evaluated. These scatter plots were visualized using the Shiny by R studio and analyzed by linear regression (including log transformation) to identify significant relationships with volume and clearance. Candidate covariates were then sequentially evaluated for inclusion in the population model.

Standard goodness-of-fit criteria were used to discriminate between candidate population models, including the Akaike information criterion (AIC) (43) and comparison of observed and predicted concentration-time plots and residual plots (population and individual), bias, and precision with the linear regression coefficient of determination. In the case of equivalent models, parsimony dictated that the simpler model be chosen. Covariates were retained in the final model if their inclusion lowered the AIC and improved the goodness-of-fit plots. Final model validation was performed by evaluating residual plots and performing a visual predictive check (VPC) of 1,000 subject simulations for each of the 32 study participants (44).

Monte Carlo simulations. A Monte Carlo simulation of 1,000 subjects was performed for each participant ($n = 32$) to evaluate the PTA after the first dose of telavancin with various dosing regimens: a 500-mg fixed dose; a 750-mg fixed dose; a 1,000-mg fixed dose; a stratified dose of 500 mg for patients with a TBW of <75 kg, 750 mg for patients with a TBW of 75 to 100 kg, and 1,000 mg for patients with a TBW of >100 kg (protocol regimen); 10 mg/kg based on ABW; and 10 mg/kg based on TBW. The predictive pharmacodynamic targets used in this analysis were *f*AUC/MIC values of 76.4 and 215. These target *f*AUC/MIC values were associated with a 1-log reduction in the number of CFU from those at the baseline for four isolates of *S. aureus* in neutropenic murine models of lung and thigh infections, respectively (11). The plasma protein binding of telavancin was assumed to be 90% (6). The PTA for the population was determined for MICs of between 0.015 and 2 mg/liter, based on the MIC_{90} values obtained in surveillance studies using the revised broth microdilution testing method and the U.S. Food and Drug Administration-approved breakpoint of ≤0.12 mg/liter for *S. aureus* (6, 45–49). In order to evaluate the potential for exposure-related toxicity in this cohort, the probability of achieving a total AUC_{0-24} value of ≥763 mg · h/liter, a value associated with acute kidney injury in patients receiving telavancin for the treatment of HABP and VABP (21), was calculated.

Safety and tolerability assessment. Safety and tolerability were assessed by clinical evaluation and laboratory or physical exam changes at 48 h postinfusion relative to the findings at the baseline. Subjects were monitored for potential adverse effects related to telavancin throughout the infusion and for the following 11 h and were queried about adverse effects at 24 and 48 h. Adverse effects were classified according to the common terminology criteria for adverse events (50).

Biomarkers of kidney injury were evaluated as early signs of renal damage. Urine samples were collected prior to infusion (baseline) and at 24 and 48 h after the start of the intravenous infusion of telavancin. A total of 13 biomarkers were measured, including kidney injury molecule-1 (KIM-1), microalbumin, calbindin, clusterin, creatinine, alpha-1-microglobulin, beta-2-microglobulin, neutrophil gelatinase-associated lipocalin, osteopontin, Tamm-Horsfall urinary glycoprotein, vascular endothelial growth factor (VEGF), trefoil factor 3 (TFF3), and cystatin C (CysC) (KidneyMAP, Myriad RBM, Austin, TX).

Statistical analysis. Noncompartmental pharmacokinetic parameters among the four body size groups were evaluated using a one-way analysis of variance (ANOVA) or the Kruskal-Wallis H test for nonnormally distributed data, and if significant differences were observed, the Tukey *post hoc* test was used with both tests. Statistical significance was based on a two-sided *P* value of <0.05, adjusting for multiple comparisons. Scatter plots were created to visually assess covariate relationships with the volume and clearance parameters generated from both noncompartmental and population analyses, with linear and polynomial regressions being performed for potentially significant parameters. A *P* value of <0.05 was considered significant for regression. One-way ANOVA was used to compare 24-h and 48-h biomarker values normalized to the baseline value for each group classified according to the BMI. Scatterplots of the values for the biomarkers to the $AUC_{0-\infty}$ and C_{max} of telavancin were generated to explore potential linear or nonlinear relationships between these subclinical markers of injury and drug exposure. Analysis of the data was performed with the SPSS (version 22; IBM Corp., Chicago, IL) and R (R Foundation, Vienna, Austria) programs.

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