



Application of physiologically based pharmacokinetic modeling to predict the pharmacokinetics of telavancin in obesity with renal impairment

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Abstract

Purpose U.S. Food and Drug Administration (FDA) recommended telavancin dosing is based on total body weight (TBW) but lacks adjusted regimens for obese subjects with varying renal function. Our aim was to develop a physiologically based pharmacokinetic (PBPK) model of telavancin to design optimized dosing regimens for obese patients with hospital-acquired pneumonia (HAP) and varying renal function.

Methods The PBPK model was verified using clinical pharmacokinetic (PK) data of telavancin in healthy populations with varying renal function and obese populations with normal renal function. Then, the PBPK model was applied to predict the PK in obese HAP patients with renal impairment (RI).

Results The fold error values of PK parameters (AUC, C_{max} , T_{max}) were all within 1.5. The telavancin AUC_{0-inf} was predicted to increase 1.07-fold in mild RI, 1.23-fold in moderate RI, 1.41-fold in severe RI, and 1.57-fold in end-stage renal disease (ESRD), compared with that in obese HAP with normal renal function. The PBPK model combined with Monte Carlo simulations (MCS) suggested that dose adjustment based on a 750-mg-fixed dose could achieve effectiveness with reduced risk of toxicity, compared with current TBW-based dosing recommendations.

Conclusion The PBPK simulation proposed that using TBW-based regimen in obesity with RI should be avoided. Dose recommendations in obesity from the PBPK model are 750 mg daily for normal renal function and mild RI, 610 mg daily for moderate RI, 530 mg daily for severe RI, and 480 mg daily for ESRD.

Keywords Physiologically based pharmacokinetic model · Telavancin · Obesity · Renal impairment · Monte Carlo simulation

Introduction

The glycopeptide antibiotic telavancin, a semi-synthetic lipoglycopeptide derived from vancomycin, is active against Gram-positive bacteria, including methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MSSA/MRSA) [1]. It is approved by the U.S. Food and Drug Administration (FDA) for treating complicated skin and skin structure infections (cSSSI), hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by *S. aureus* when

alternative treatments are not suitable [2]. Telavancin dosing is based on total body weight (TBW) [2].

Telavancin is not absorbed orally, only intravenously. In healthy young adults, telavancin displays linear pharmacokinetics (PK) following single doses from 5 to 12.5 mg/kg and multiple doses from 7.5 to 15 mg/kg administered once daily for up to 7 days. Steady-state concentrations are achieved on the third day [2]. Telavancin has a high protein-binding rate (90%) and is not affected by renal impairment (RI) [2, 3]. It is mainly eliminated by renal excretion. In a single-dose radiolabeled telavancin study in healthy subjects, 76% of the dose was recovered in the urine and only 1% in feces. Forty-eight hours post-administration, most of the dose in the urine (83%) was excreted unchanged (63.08%) [1, 4]. Telavancin metabolism does not involve the hepatic cytochrome P450 (CYP) enzyme system, but its metabolic pathway has not been determined [2]. The mass balance calculation indicates that up to 30 to 37% of the dose is metabolized within 216 h post-administration [4].

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Although telavancin is generally well tolerated, the risk of nephrotoxicity should be considered [3]. Several studies demonstrated that telavancin administration increases serum creatinine levels, indicating its potential nephrotoxicity [5–7]. Renal adverse events were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction (pre-existing renal disease, diabetes mellitus, congestive heart failure, or hypertension). Moreover, there was an increase in mortality in patients with HAP/VABP and pre-existing moderate-to-severe RI (CrCl ≤ 50 mL/min) [2]. Expose-response relationships for safety suggested that a total AUC from time zero to 24 h (AUC_{0–24}) of ≥ 763 mg · h/L was associated with a higher acute kidney injury rate than a total AUC_{0–24} of < 763 mg · h/L [8].

Obesity is recognized as a global pandemic by the World Health Organization (WHO), and approximately 60% of the world's population will be classified as overweight or obese by 2030, according to the body mass index (BMI) scale [9]. Physiological changes in obesity commonly affect the PK and pharmacodynamics (PD) of telavancin and may lead to suboptimal dosing in this expanding but under-researched population. Renal events occurred 2.8 times more often in patients with BMI ≥ 35 kg/m² than in patients with BMI < 35 kg/m² [10]. PK modeling and Monte Carlo simulations (MCS) suggested a fixed dose of 750 mg every 24 h should be equally effective and less toxic for the treatment of obese patients with normal renal function and *S. aureus* infections compared with 10 mg/kg every 24 h based on TBW. If higher systemic exposure in plasma concentrations is desired in obese subjects, a maximum dose of 1000 mg should be considered [8].

Obesity is associated with an increased risk of chronic kidney disease (CKD), which is also a public health problem [11, 12]. The aggravation of renal damage in CKD increases the antibiotic's area under the plasma concentration-time curve (AUC) and half-time ($t_{1/2}$) associated with a decrease in clearance (CL) [13]. Similar to obese patients with normal renal function, the FDA-recommended dosing levels based on TBW may also be too high, leading to toxicity in obese patients with different degrees of RI. Thus, it is necessary to design optimized dosing regimens for obese patients with different renal function.

To date, there is no PK study focused on the obese population with RI, although optimal telavancin dosing is challenging in these patients. In recent years, physiologically based pharmacokinetic (PBPK) modeling has emerged as a valuable tool for evaluating drug exposure in virtual populations and obtaining mechanistic insights into drug characteristics by integrating key drug and system parameters into a dynamically interconnected model that can improve guidance on dosing in a special population [14]. Specifically, we conducted this study to build and verify a PBPK model that could predict the PK of telavancin in obese hospital-acquired pneumonia

(HAP) patients with different degrees of RI, maximizing the antibiotic's efficacy and safety.

Methods

PBPK model development

The PBPK modeling and simulations of telavancin were conducted using GastroPlus™ v.9.7 (Simulations Plus Inc., Lancaster, CA). The observed concentration-time profiles were captured directly by digitization (GetData Graph Digitizer 2.26) from the figures. MCS were performed using the Oracle Crystal Ball software (Oracle Co., Redwood Shores, CA).

The setting for modeling parameters and structure are presented in [Supplementary Methods](#). The overall strategy for the development, verification, and application of the PBPK model for telavancin is presented as a workflow diagram in [Fig. 1](#).

Model validation

The telavancin PBPK model was verified using clinical PK data from the literature [4, 8, 13, 15–18], as shown in [Supplemental Table S2](#). The detailed simulation steps for verification are described in [Supplementary Methods](#). The prediction accuracy was graphically evaluated by superimposing the concentration-time profile observed in vivo on the simulated data. The accuracy of predicted PK parameters (AUC, C_{max} , T_{max}) was assessed by calculating the fold error as the predicted-to-observed PK parameter ratio, with an acceptable prediction being within a 2-fold error.

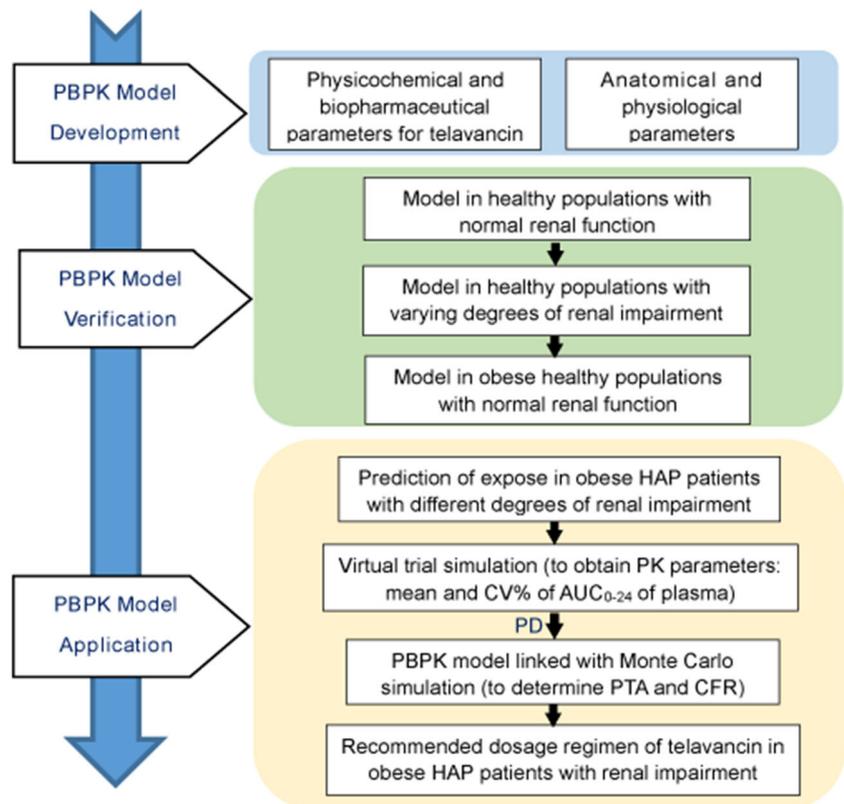
PBPK model application

Population PK analyses from the literature demonstrate the similarity of the PK of telavancin among healthy subjects, patients with cSSSI, and patients with HAP [19]. Therefore, the telavancin PBPK model in healthy populations was used to predict the PK in HAP patients. The changes of AUC from time zero extrapolated to infinity (AUC_{0–inf}) in obese (classes I, II, III) HAP patients with varying degrees of RI after a fixed dose of 1000 mg intravenous infusion over 1 h were predicted. The detailed methods for prediction are described in [Supplementary Methods](#). Using the same drug administration regimen, the AUC ratio (AUCR) values of different obesity classes were calculated using [Eq. 1](#).

$$\text{AUCR} = \frac{\text{AUC}_{\text{RI}}}{\text{AUC}_{\text{Control}}} \quad (1)$$

where AUC_{RI} and AUC_{Control} are the AUC in RI subjects and AUC in patients without RI, respectively.

Fig. 1 Workflow of PBPK model. HAP, hospital-acquired pneumonia; PTA, probability of target attainment; CFR, cumulative fraction of response



The mean AUCR of three obesity classes was used to provide dose regimen recommendations in 30-year-old obese American male patients with HAP and different RI.

The population simulation was carried out. Similar to the obesity, the population was set as 18–50 years old, 50% male, BMI 30–50, TBW 90–154 kg, and sample sizes of 200 [8]. AUC_{0-24} mean and standard error (SD) values were analyzed for obese HAP patients with different renal functions after various dosing regimens: fixed doses and the FDA-recommended regimen (e.g., for normal renal function: 750 mg fixed dose; 1000 mg fixed dose; 10 mg/kg based on TBW).

MCS were performed with 50,000 patients to evaluate the probability of target attainment (PTA) and the cumulative fraction of response (CFR). The 24-h unbound (free) area under the concentration–time curve ($fAUC_{0-24}$)-to-minimum inhibitory concentration (MIC) ratio ($fAUC_{0-24}/MIC$) values of 76.4 and 215 were the predictive PD targets, which were associated with a 1-log reduction in the number of colony-forming units (CFUs) from the baseline CFUs for four isolates of *S. aureus* in neutropenic murine models of lung and thigh infections, respectively [20]. The plasma protein binding of telavancin was assumed to be 90% [3]. The MIC data of *S. aureus* (MSSA/MRSA) were extracted from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [1]. The FDA-approved telavancin breakpoint is ≤ 0.12 mg/L for *S. aureus* [8], and the MIC value required to

inhibit the growth of 90% of *S. aureus* isolates (MIC_{90}) is 0.06 mg/L [1]. 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/L was calculated. Finally, the telavancin-dosing regimen for obese HAP patients with varying degrees of RI was determined to maximize the PTA while minimizing the risk of reaching a threshold of exposure associated with nephrotoxicity.

Results

Development and validation of the PBPK model in healthy populations

The observed and the PBPK model–simulated mean plasma concentration–time profiles of telavancin were derived from healthy populations after administering a 10 mg/kg single-dose intravenous infusion, and 7.5 mg/kg and 10 mg/kg multiple-dose intravenous infusions (Supplemental Fig. S1). Importantly, the predicted and observed plasma concentration–time profiles had matching profiles. The predicted PK parameters (AUC , C_{max} , T_{max}) were generally consistent (< 1.3 -fold error) with the observed values, except that the predicted AUC values on day 3 of 7.5 mg/kg and 10 mg/kg of intravenous infusion over 1 h every 24 h were smaller than the observed values (< 1.5 -fold error), as shown in Supplemental Table S3.

Development and validation of the PBPK model in healthy populations with varying degrees of RI

The simulated and measured plasma concentrations shared matching profile shapes in healthy populations with varying degrees of renal function after administering single intravenous telavancin infusions of 7.5 mg/kg and 10 mg/kg (Supplemental Fig. S2). The predicted PK parameters (AUC, C_{max}) were reasonably consistent (<1.3-fold error) with the observed values, except that the predicted AUC values for 7.5 mg/kg telavancin in subjects with severe RI were smaller than the observed values (1.32-fold error), as shown in Supplemental Table S4. The T_{max} predictions of 1 h were consistent with the observed values.

Relative changes in telavancin PK were compared between healthy populations and different renal function states (Supplemental Table S4), which shows that our model could accurately capture the increasing trend of telavancin AUC with the increasing severity of RI. The predicted CL_R , $CL_R/CL(\%)$, and $CL_h/CL(\%)$ were similar to the observed values, as shown in Supplemental Table S5, indicating that RI might not affect CL_h greatly and the PBPK model was reliable. GFR

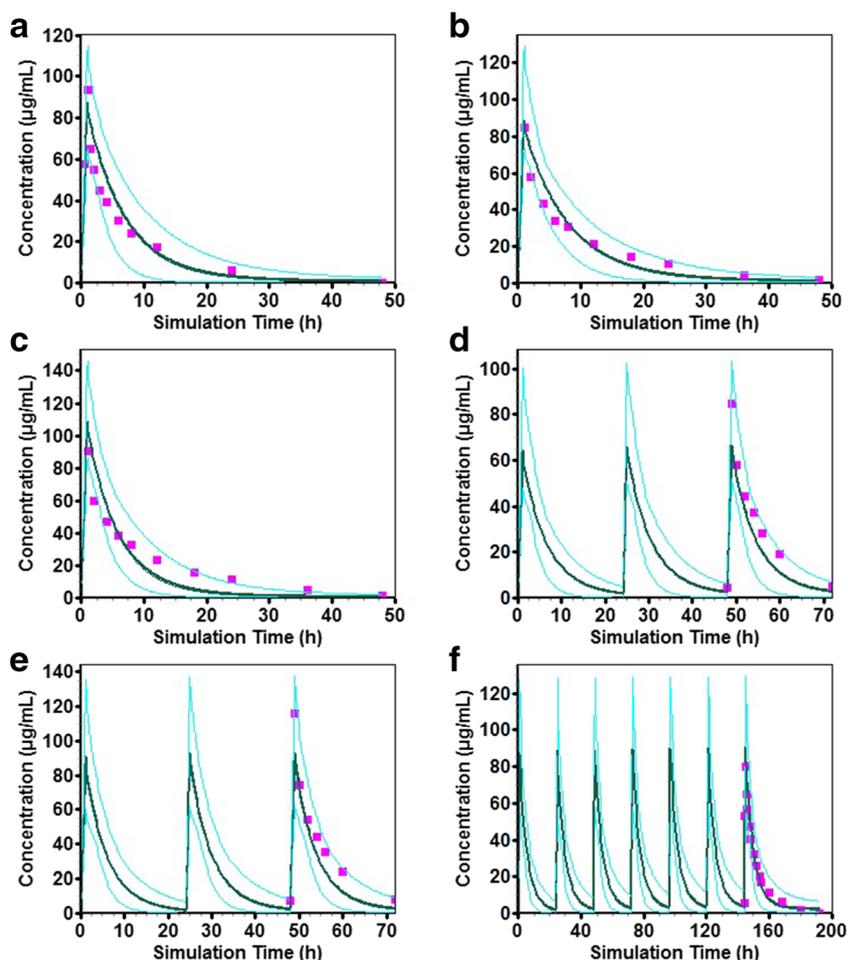
decreased with an increase in the degree of RI severity, leading to the decline of CL_R and CL_R/CL . However, in the hepatic metabolism, the contribution of the non-CYP-mediated metabolism to CL (CL_h/CL) increased.

Development and validation of the PBPK model in obese healthy populations with normal renal function

The PK parameters (AUC, C_{max}) of telavancin in obese healthy populations with normal renal function after various fixed dosing regimens by PBPK modeling corresponded well (<1.3-fold error) with the observed values (Supplemental Table S6). The T_{max} predictions of 1 h were consistent with the observed values.

A comparison of the relative changes in PK, which was based on the 1000-mg dosage (Supplemental Table S6), reproduced the similarity of exposure in different classes of obesity. The model-simulated V_{ss} , CL, and CL_R are shown in Supplemental Table S7, indicating that V_{ss} increased with obesity, whereas simulated CL and CL_R values did not differ among the four weight classes.

Fig. 2 Population simulation for healthy populations after administering telavancin as a single-dose intravenous infusion of 10 mg/kg (a–c) [4, 15] and multiple-dose intravenous infusions of 7.5 mg/kg (d) [16] and 10 mg/kg (e, f) [17, 18]. A solid black line adjacent to the middle of the concentration–time profile represents the mean of the predicted values. Solid squares represent the observed clinical concentration–time data. The thin lines on either side represent individual simulated results that include 100% of the range of simulated individual data



Population simulation

The population simulation results of healthy subjects with different renal functions are presented in Fig. 2 and Fig. 3. Specifically, we found that all observed data were within the minimal and maximal individual subject simulations from the population simulations (i.e., 100% probability), except the predicted plasma concentration–time curves in subjects with severe RI, which were slightly lower than the observed concentration points. Furthermore, the fold error of AUC in subjects with severe RI was less than 1.5 (Supplemental Table S8), indicating acceptable recovery of clinical data by the model.

PBPK model application

The AUC_{0-inf} and AUCR of different obesity classes were simulated under the same drug administration regimen (1000 mg intravenous infusion over 1 h) (Supplemental Table S9). The calculated mean AUCR of the three obesity classes are presented in Supplemental Table S9. A comparison of the exposure simulations among the different RI levels indicated that exposure to telavancin increased with an increase in the degree of RI severity. The AUC_{0-inf} for telavancin was predicted to increase 1.07-fold in mild RI, 1.23-fold in moderate RI, 1.41-fold in severe RI, and 1.57-

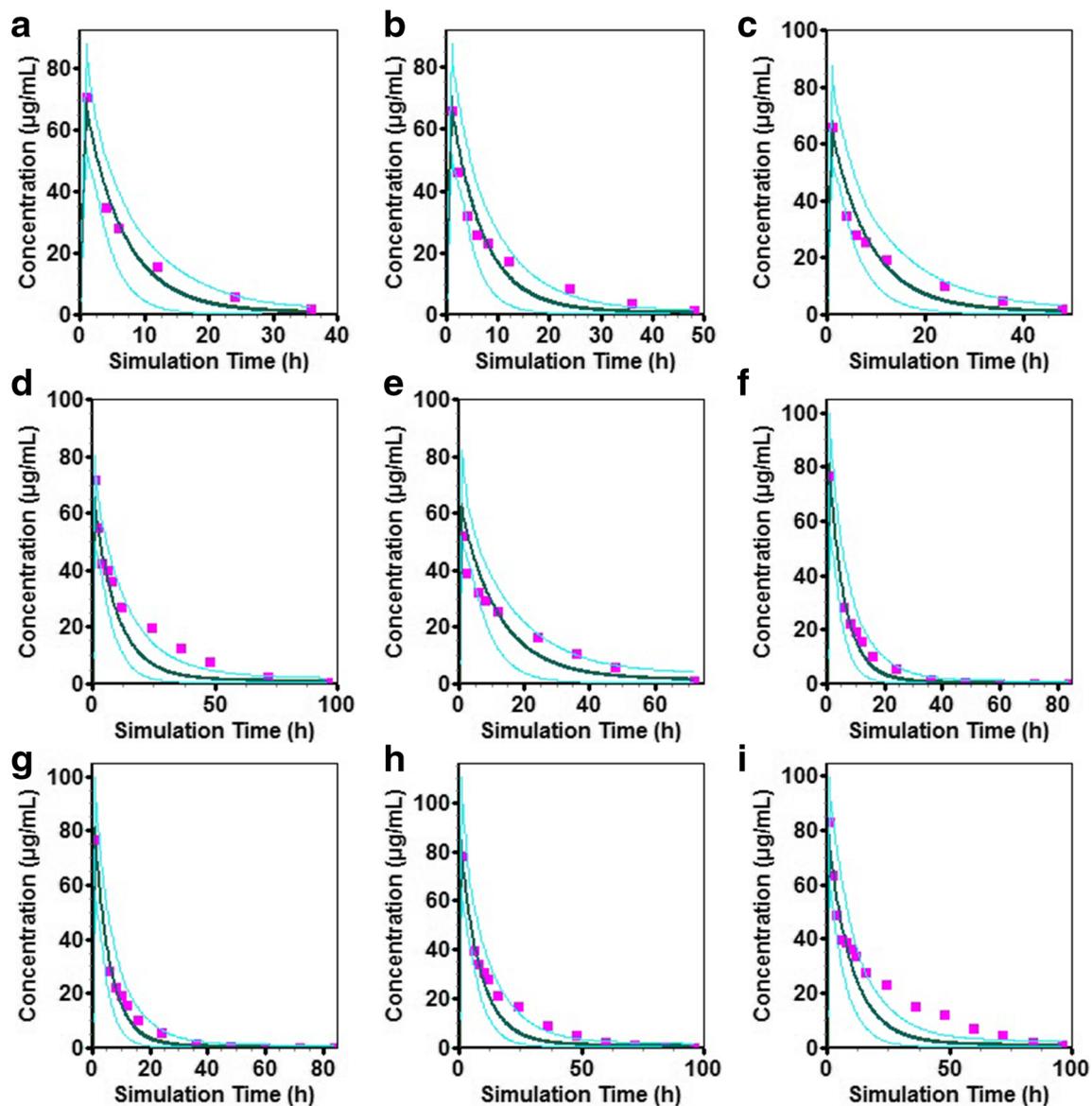


Fig. 3 Population simulation for healthy populations with normal renal function (a, f), mild renal impairment (RI) (b, g), moderate RI (c, h), severe RI (d, i), and ESRD (e) after administering 7.5 mg/kg (study A) and 10 mg/kg (study B) [13] single-dose intravenous infusion. A solid black line adjacent to the middle of the concentration-time profile

represents the mean of the predicted values. Solid squares represent the observed clinical concentration–time data. The thin lines on either side represent individual simulated results that include 100% of the range of simulated individual data

fold in ESRD, compared with that in obese HAP patients with the normal renal function (Supplemental Table S9).

Obese HAP patients with mild RI are unlikely to require dose adjustments. However, there might be a need for dose adjustment across moderate and severe RI or ESRD populations after receiving the same dose. The administration regimen in obese HAP patients with normal renal function was 750 mg or 1000 mg, but the different degrees of RI required corresponding dose adjustments (Supplemental Table S10). The mean and SD of AUC_{0-24} in obese HAP patients with different renal functions after various dosing regimens (fixed

doses and FDA-recommended regimen) are shown in Supplemental Table S10.

The results of the 50,000-patient MCS are shown in Table 1. The target attainment rate for the 24-h $fAUC/MIC$ ratio breakpoint of 76.4 was 100% for all telavancin dosage regimens (fixed and weight-based) when the MIC values were ≤ 0.25 mg/L. When the breakpoint of 215 was evaluated, the 1000-mg-fixed dose regimen and FDA-recommended regimen (based on TBW) achieved a target attainment rate of 100% when the MIC values were ≤ 0.125 mg/L. Furthermore, the 750-mg-fixed dose regimen also achieved a target attainment

Table 1 Probability of target attainment (PTA) of different telavancin dosage regimens in obese patients with HAP and varying degrees of renal impairment (RI)

Target	Renal function state	Dose (mg)	Attainment of PTA (%) for MIC ($\mu\text{g/mL}$)	
			0.125	0.25
Dose adjustment based on 1000-mg-fixed dose				
$fAUC_{0-24}/MIC > 76.4$	Normal	1000 qd	100	100
	Mild	1000 qd	100	100
	Moderate	810 qd	100	100
	Severe	710 qd	100	100
	ESRD	635 qd	100	100
$fAUC_{0-24}/MIC > 215$	Normal	1000 qd	100	75.47
	Mild	1000 qd	100	86.93
	Moderate	810 qd	100	75.53
	Severe	710 qd	100	66.07
	ESRD	635 qd	100	56.11
Dose adjustment based on 750-mg-fixed dose				
$fAUC_{0-24}/MIC > 76.4$	Normal	750 qd	100	100
	Mild	750 qd	100	100
	Moderate	610 qd	100	100
	Severe	530 qd	100	100
	ESRD	480 qd	100	100
$fAUC_{0-24}/MIC > 215$	Normal	750 qd	99.96	11.65
	Mild	750 qd	99.98	19.70
	Moderate	610 qd	99.97	8.46
	Severe	530 qd	99.90	4.43
	ESRD	480 qd	99.98	1.32
FDA-recommended regimen (based on TBW)				
$fAUC_{0-24}/MIC > 76.4$	Normal	10 mg/kg q24h	100	100
	Mild	10 mg/kg q24h	100	100
	Moderate	7.5 mg/kg q24h	100	100
	Severe	10 mg/kg q48h	100	100
	ESRD	-	-	-
$fAUC_{0-24}/MIC > 215$	Normal	10 mg/kg q24h	100	84.19
	Mild	10 mg/kg q24h	100	89.07
	Moderate	7.5 mg/kg q24h	100	61.20
	Severe	10 mg/kg q48h	100	99.85
	ESRD	-	-	-

qd, once daily; q24h, every 24 h; q48h, every 48 h; $fAUC_{0-24}/MIC$, 24-h unbound (free) area under the concentration-time curve ($fAUC_{0-24}$)-to-minimum inhibitory concentration (MIC) ratio; ESRD, end-stage renal disease

rate of 99.9% for MIC values of ≤ 0.125 mg/L. When the MIC value was 0.25 mg/L in severe RI, only 10 mg/kg every 48 h resulted in target attainment rates of $> 90\%$ for the 24-h fAUC/MIC ratio of 215. Under the three dosing regimens, the CFR of telavancin against MSSA and MRSA in obese HAP patients with varying degrees of RI were all $> 99.9\%$ (Table 2).

The probabilities of attaining a toxicodynamic target (total AUC_{0-24} value of ≥ 763 mg · h/L) in obese HAP patients with varying degrees of RI are shown in Table 3. The lowest probability of almost 0% was associated with the 750-mg-fixed dose regimen, compared with those associated with the

1000-mg-fixed dose and FDA-recommended regimens. According to FDA labeling and the PBPK model, telavancin dosage regimens for normal-body-weight and obese HAP patients with varying degrees of RI are listed in Table 4.

Discussion

This is the first study to develop a PBPK model for telavancin in healthy populations with different renal functions (normal

Table 2 Cumulative fraction of response % (CFR%) of telavancin against MSSA and MRSA in obese HAP patients with varying degrees of renal impairment (RI)

Target	Renal function state	Dose(mg)	Cumulative fraction of response % (CFR %)		
			MSSA	MRSA	
Dose adjustment based on 1000-mg-fixed dose					
fAUC ₀₋₂₄ /MIC >76.4	Normal	1000 qd	100	100	
	Mild	1000 qd	100	100	
	Moderate	810 qd	100	100	
	Severe	710 qd	100	100	
	ESRD	635 qd	100	100	
	fAUC ₀₋₂₄ /MIC >215	Normal	1000 qd	100	99.98
		Mild	1000 qd	100	99.99
		Moderate	810 qd	100	99.99
		Severe	710 qd	99.99	99.98
		ESRD	635 qd	100	99.97
Dose adjustment based on 750-mg-fixed dose					
fAUC ₀₋₂₄ /MIC >76.4	Normal	750 qd	100	100	
	Mild	750 qd	100	100	
	Moderate	610 qd	100	100	
	Severe	530 qd	100	100	
	ESRD	480 qd	100	100	
	fAUC ₀₋₂₄ /MIC >215	Normal	750 qd	99.97	99.94
		Mild	750 qd	99.97	99.94
		Moderate	610 qd	99.97	99.94
		Severe	530 qd	99.96	99.94
		ESRD	480 qd	99.96	99.94
FDA-recommended regimen (based on TBW)					
fAUC ₀₋₂₄ /MIC >76.4	Normal	10 mg/kg q24h	100	100	
	Mild	10 mg/kg q24h	100	100	
	Moderate	7.5 mg/kg q24h	100	100	
	Severe	10 mg/kg q48h	100	100	
	ESRD	-	-	-	
	fAUC ₀₋₂₄ /MIC >215	Normal	10 mg/kg q24h	100	100
		Mild	10 mg/kg q24h	100	100
		Moderate	7.5 mg/kg q24h	100	99.99
		Severe	10 mg/kg q48h	100	100
		ESRD	-	-	-

qd, once daily; q24h, every 24 h; q48h, every 48 h; fAUC₀₋₂₄/MIC, 24-h unbound (free) area under the concentration-time curve (fAUC₀₋₂₄)-to-minimum inhibitory concentration (MIC) ratio; ESRD, end-stage renal disease

Table 3 The probability of achieving the total AUC_{0-24} value of ≥ 763 mg · h/L in different dosing regimens

Renal function state	Dose(mg)	Probability (%)
Dose adjustment based on 1000-mg fixed dose		
Normal	1000 qd	5.45
Mild	1000 qd	12.29
Moderate	810 qd	3.19
Severe	710 qd	1.54
ESRD	635 qd	0.45
Dose adjustment based on 750-mg-fixed dose		
Normal	750 qd	0.02
Mild	750 qd	0.09
Moderate	610 qd	0
Severe	530 qd	0
ESRD	480 qd	0
FDA-recommended regimen (based on TBW)		
Normal	10 mg/kg q24h	11.12
Mild	10 mg/kg q24h	17.29
Moderate	7.5 mg/kg q24h	1.68
Severe	10 mg/kg q48h	77.85
ESRD	-	-

qd, once daily; q24h, every 24 h; q48h, every 48 h; ESRD, end-stage renal disease

renal function, mild, moderate, severe RI, and ESRD) and obese adults with varying degrees of renal function.

During the model development, CL_R was calculated as $GFR \times f_{up}$. The predicted CL_R values were reasonably consistent with the observed values, indicating that the contribution of other factors combined, including transporter-mediated renal tubular secretion and tubular reabsorption, might not be important for renal excretion of telavancin.

For subjects without RI or with RI, CL_h was always defined as the half of CL_R in individuals with normal renal

function. Telavancin distribution to tissues is expected to occur in a permeability-limited manner due to the drug's moderate lipophilicity and large size. When all tissues were set as permeability-limited tissues, GastroPlus™ assigned an upper limit for CL_h that was much less than one half of the CL_R value. Under this condition, the amount of telavancin entering the liver would be very small, and the prediction for AUC_{inf} would generate a much larger value. This suggested that the liver might have a potential uptake transporter for telavancin besides passive diffusion. Since there is no published report on the hepatic transporter-mediated uptake of telavancin to date, we could not improve the simulation. However, when the liver was set as a blood perfusion-limited tissue, which means more drugs can enter the liver for metabolism, the prediction accuracy of the model was much higher. The involvement of a potential uptake transporter for telavancin in the liver needs to be further explored in the future.

RI can cause PK changes, which in turn affect the efficacy and even increase the risk of adverse reactions. Based on the PBPK model for healthy populations, the physiological parameters subject to alteration in response to RI were changed. Telavancin systemic exposure (AUC_{inf}) increased with the severity of RI. GFR decreased in subjects with RI, leading to the decline of CL_R and CL_R/CL . CL_h might not change greatly with the degree of severity of RI. However, due to the decrease of CL in subjects with RI, especially in the case of severe RI, the CL_h/CL ratio increased greatly, and therefore, the contribution of non-CYP-mediated metabolism to CL was greatly increased in subjects with severe RI. There are no specific dosage adjustment recommendations for patients with ESRD ($CrCl < 10$ mL/min), including patients undergoing hemodialysis (HD) [2]. Thus, our PBPK model can be used to predict the PK of telavancin in subjects with ESRD.

The FDA has no specific dosing regimen for obese subjects with different renal functions. Clinical experience using telavancin in these populations is limited.

Table 4 Telavancin dosage regimens for normal-body-weight and obese HAP patients with varying degrees of renal impairment (RI)

Category	BMI (kg/m ²)	TBW (kg)	Renal function state	Dose(mg)
Normal to overweight	18.5–29.9	50–99.9	Normal	10 mg/kg q24h
			Mild	10 mg/kg q24h
			Moderate	7.5 mg/kg q24h
			Severe	10 mg/kg q48h
			ESRD	-
Obesity	30–50	90–154	Normal	750 qd
			Mild	750 qd
			Moderate	610 qd
			Severe	530 qd
			ESRD	480 qd

BMI, body mass index; TBW, total body weight; qd, once daily; q24h, every 24 h; q48h, every 48 h; ESRD, end-stage renal disease

We established and validated the telavancin PBPK model for obese healthy populations with normal renal function. The successful validation of the PBPK model in obesity supports that V_{ss} of telavancin was the only PK parameter that tended to increase with body weight, and there is no physiological mechanism for enhanced elimination [8].

To evaluate the effect of inter-individual variability of population physiology parameters on the simulation results, we combined telavancin PK study with population simulations. The advantage of the MCS-based PBPK approach is that it facilitates the projection of the population mean of the PK characteristics as well as the variability, which will enable us to better anticipate the clinical reality. Population simulations were not carried out on obese healthy populations with normal renal function, due to the lack of observed plasma concentration–time profiles.

This model was applied for the first time to predict the PK of telavancin in obesity HAP with varying degrees of RI. Obese HAP patients with mild RI are unlikely to require dose adjustments. There may be a need for dose adjustment across the moderate-to-severe RI or ESRD populations after the initial administration of the recommended dose.

The PBPK model, combined with MCS, was used to predict the optimal PTA against *S. aureus* at or below the MIC breakpoint with a low probability of nephrotoxicity. We found that both fixed doses (dose adjustment based on 1000 mg fixed dose and on 750 mg fixed dose) attained the same PK-PD targets of efficacy as the FDA-recommended regimen based on TBW. Furthermore, the simulation indicated that the TBW-based regimen uses higher doses that lead to more toxicity. Dose adjustment based on the 750 mg fixed dose has a lower potential (almost 0%) to lead to exposures exceeding 763 mg · h/L than other dosing regimens in obesity with RI.

Our PBPK model also has some limitations in relation to validation data, the mechanism of telavancin distribution and clearance, ranges of age and weight among obesity subjects, and the evaluation of predictive performance. The detailed limitations are described in [Supplementary Discussion](#).

Conclusion

In this study, a PBPK model of telavancin was developed to simulate the telavancin PK in healthy populations with varying degrees of renal function and obese subjects with normal renal function. The PBPK model was further extrapolated to generate predictions for obese HAP patients with RI. Our simulation suggests that dose adjustment based on the 750-mg-fixed dose can achieve effectiveness with a lower risk of toxicity than the current TBW-based dosing recommendation.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00228-020-03072-y>.

Code availability The databases of modeling are available from the corresponding author upon reasonable request.

Author' contributions CL designed the study and drafted the article. WW and CL discussed the study and drafted the article. WW, MK, and LY performed the study. WW and MK participated in data analysis. MK revised the article.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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