DR JILL BUTTERFIELD-COWPER (Orcid ID : 0000-0002-6497-7908)

DR AMIT PAI (Orcid ID : 0000-0001-7119-5034)

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A Fixed versus Weight-Based Dosing Strategy of Daptomycin may Improve Safety in Obese Adults

Jill M. Butterfield-Cowper[1], Thomas P. Lodise, Jr.[2], Manjunath P. Pai[3*]

[1]HealthTrust Supply Chain, Richmond, VA, USA

[2]Albany College of Pharmacy and Health Sciences, Albany, NY, USA

[3]College of Pharmacy, University of Michigan, Ann Arbor, MI, USA

Running Title: Fixed Dosing Daptomycin in Obesity

*Correspondence: Manjunath (Amit) P. Pai
College of Pharmacy
University of Michigan
Rm 3569, 428 Church St, Ann Arbor, MI 48108
Tel: 734-647-0006 (COP)
Email: amitpai@med.umich.edu

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Abstract

OBJECTIVES: To compare daptomycin exposures and predicted safety outcomes with a simulated weight-based and fixed dose in morbidly-obese and non-obese subjects

METHODS: We performed a nonparametric population pharmacokinetic analysis of daptomycin concentration-time data from a prior obese and non-obese kidney function matched cohort of healthy adult volunteers. Monte Carlo simulations were performed to compare the maximum concentrations (C_{max}), minimum concentrations (C_{min}), and area under the curve (AUC) with the standard daptomycin 6-mg/kg/day dose or a 500-mg daily fixed dose in obese and non-obese subjects. The probability of exceeding a daptomycin C_{min} target (≥ 24.3 mg/L) associated with creatine phosphokinase (CPK) elevations was computed with the two regimens.

RESULTS: There were no significant differences in clearance (CL), volume of distribution at steady state (V_{ss}), or terminal half-life ($t_{1/2}$) between the morbidly-obese and non-obese PK models. Daptomycin 6 mg/kg/day resulted in AUC, C_{max}, and C_{min} values that were approximately 2-fold higher in morbidly-obese subjects relative to non-obese individuals. In contrast, fixed dosing (500 mg/day) resulted in relatively isometric exposures. The fraction of simulated morbidly-obese subjects with a C_{min} target associated with CPK elevations was 10.8% with 6 mg/kg/day and 2.0% at the 500-mg/day dosage.

CONCLUSIONS: Weight-based maintenance dosing of daptomycin is less likely to yield bioequivalent exposures in morbidly-obese subjects and provides credence for evaluation of fixed maintenance doses across adult body size to improve safety.**INTRODUCTION**

Daptomycin, a key antimicrobial in our armamentarium against Methicillin-resistant *Staphylococcus aureus* (MRSA), is dosed on total body weight (TBW), regardless of patient's weight. Currently, no dose adjustments or dosing caps are recommended for patients who are either overweight or obese [1]. When the decision is made to dose an antibiotic on TBW, there are two major assumptions: i) key pharmacokinetic (PK) parameters, namely drug clearance (CL) and volume of distribution (V), change proportionately with TBW and ii) TBW-based dosing is necessary to achieve isometric plasma-concentration time profiles across the continuum of weights. Since drug exposure is inversely related to drug CL, dosing on TBW will lead to higher exposures in obese patients if CL does not increase in proportion to TBW. Although this is a well-recognized pharmacologic concept, we lack quantitative evaluations of whether weight-based daptomycin dosing schemes achieve isometric exposure profiles across the weight continuum. Lack of information regarding the appropriateness of daptomycin weight-based dosing is concerning because some experts recommend use of even higher weight-based doses (8-12 mg/kg on TBW) of daptomycin that may not be appropriate for two-thirds of adults in the United States who are either overweight or obese [2-5].

The primary objective of this investigation was to determine whether weight-based dosing of daptomycin results in equivalent exposures in morbidly-obese and non-obese subjects. The secondary objective was to evaluate the utility of fixed dosing among morbidly-obese and non-obese subjects.

MATERIALS AND METHODS

Study Population

The plasma concentration-time data for daptomycin in morbidly-obese (Body Mass Index (BMI)> 40 kg/m^2) and non-obese (BMI 18-25 kg/m^2) subjects matched on age, sex, race, and serum creatinine (SCr) were obtained from a previous study [6]. Blood samples were collected prior to a single 4-mg/kg dose of daptomycin and at 0.5 (end of infusion), 1.0, 1.5, 2.0, 4.0, 8.0, 12.0, and 24 hours from the start of infusion; plasma was assayed using a validated high-performance liquid chromatography method [6]. The glomerular filtration rate (GFR) was measured in each subject using ^{125}I-sodium iothalamate.

Population PK Modeling

All data were analyzed in a population PK model using the big nonparametric adaptive grid (BigNPAG) program, as previously described [7]. Plasma PK data from morbidly-obese and non-obese subjects were modeled separately and each model was parameterized as a two-compartment model with zero-order infusion and elimination from the central-compartment as a first-order elimination process. Upon attaining convergence, Bayesian estimates for each patient were obtained using the "population of one" utility within BigNPAG for each model. After the Bayesian step, goodness of fit and predictive performance were assessed [8].

Median PK parameter estimates from the morbidly-obese and non-obese PK models were compared by the Mann-Whitney U test. Linear regression was used to determine the association between individual Bayesian estimates of daptomycin CL and volume of distribution of the central compartment (V_c) and TBW. All calculations were computed with SYSTAT for Windows (Version 11.0) or SPSS version 12.0.1 (SPSS, Chicago, IL).

Monte Carlo simulation

For both PK models (non-obese and morbidly-obese), 9999 subject simulations were performed for TBW-based dosing (6 mg/kg/day) and fixed dosing (500 mg/day). This fixed dose was selected since daptomycin is formulated in 500-mg vials and represents a similar central tendency dose that would be calculated in an average US adult (80-85 kg). For each simulation, the area under the concentration-time curve between 0 and 24 hours at steady state ($AUC_{0\text{-}24SS}$), maximum concentration at steady state 0.5 hours after the end of infusion (C_{maxss}), and minimum concentration at steady state (C_{minss}) were determined. The probability of exceeding C_{minss} of 24.3 mg/L or greater was calculated as this has been identified as the pharmacodynamic (PD) threshold associated with creatine phosphokinase (CPK) elevation [9]. The population simulation without process noise option was utilized and log-normal distributions of PK parameters were selected for all simulations.

Results

Details of population demographics have been described previously [6]. Briefly, the morbidly-obese (n=7) and non-obese (n=7) groups were well matched for age, race, SCr, GFR, and all subjects were female. The mean (standard deviation) age, BMI, SCr, and measured GFR was 36.8 (29.1)/29.1 (12) years, 46.2 (5.5)/21.8(1.9) kg/m^2, 0.8 (0.2)/0.8 (0.1) mg/dl, and 116 (45.2)/ 93.5 (13.4) ml/min in the morbidly-obese/non-obese subjects, respectively. The mean (standard deviation) population parameter estimates for the morbidly-obese and non-obese population PK models are displayed in Table 1. Using the population mean parameter values as the measure of central tendency, the overall fit of the models to their respective data after the Bayesian step were good (R^2>0.98) and the plots of predicted versus observed concentrations showed slopes and intercepts very close to the ideal values of 1.0 and 0.0, respectively.

There were no significant differences in CL, V_c, volume of distribution at steady state (V_{ss}), or terminal half-life ($t_{1/2}$) between the morbidly-obese and non-obese PK models. Significant differences, however, in intercompartmental transfer rate constants (K_{cp} and K_{pc}) values between morbidly-obese and non-obese subjects were noted (Table 1). However, V_{ss}, which is derived from the ratio of K_{cp} to $K_{pc,}$ was not significantly different between the groups. No significant associations were observed in the linear regression analysis that examined the relationship between individual Bayesian estimates of daptomycin CL and V_c with TBW (Figure 1).

In the Monte Carlo simulation analyses, TBW-based dosing (6 mg/kg/day) resulted in $AUC_{0\text{-}24SS}$, C_{maxss}, and C_{minss} values that were approximately 2-fold higher in morbidly-obese subjects relative to non-obese individuals (Table 2). In contrast, fixed dosing (500 mg/day) resulted in relatively isometric $AUC_{0\text{-}24SS}$, C_{maxss}, and C_{minss} values between groups. The fraction of simulated morbidly-obese subjects with a C_{minss} of 24.3 mg/L or greater was 10.8% given TBW-based dosing and 2.0% given fixed dosing. For non-obese subjects, the percentage with a C_{minss} of 24.3 mg/L or greater was 0.2% with both dosing regimens.

DISCUSSION

Since daptomycin is dosed on TBW, one should expect that CL and V_c change proportionately with TBW to ensure similar exposure profiles [4]. However, our estimates of CL and V_c were similar for morbidly-obese and non-obese subjects. Furthermore, no association was noted between individual Bayesian PK estimates and TBW upon linear regression (Figure 1). These findings were reflected in the Monte Carlo simulation, where a TBW-based daptomycin dose of 6 mg/kg/day yielded $AUC_{0\text{-}24SS}$, C_{maxss}, and C_{minss} values that were nearly 2-fold higher in morbidly-obese subjects relative to non-obese subjects. Since CL and V_c were not found to be different between groups, the larger total doses used in obese subjects resulted in the more robust exposure profiles in the obese-simulated population. In contrast, fixed dosing (500 mg/day) resulted in relatively isometric exposure profiles since CL and V_c were nearly identical between groups.

Our findings are largely consistent with previous publications and mathematical expectations [10]. Dvorchik and Damphousse also reported higher daptomycin exposures in obese versus non-obese subjects [11]. Yet, in contrast to our findings, they noted that total CL and V_{ss} significantly increased by approximately 20% in obese subjects [11]. It is important to note that these subjects were not adequately matched for kidney function as the researchers relied on creatinine clearance computed with TBW, obscuring the ability to assess the relationship between CL and V_{ss} with TBW [10]. Furthermore, a comprehensive population PK model that included the Dvorchik and Damphousse results failed to demonstrate an independent association between daptomycin CL and V_c with TBW [12].

Our findings have major implications for clinical practice. First, the exaggerated exposures observed among morbidly-obese subjects suggest that TBW may increase the risk of non-immunologic exposure-related toxicities in patients with obesity, especially those related to higher daptomycin troughs and AUCs. In particular, obese individuals may be at greater risk for CPK elevations since this toxicity appears to be related to higher daptomycin trough levels. Of note, most of the patients who experienced a CPK elevation in the daptomycin S. aureus bacteremia and infective endocarditis trial were obese [13], substantiating the clinical implications of our findings. Other researchers have also reported that two out of three

patients with musculoskeletal symptoms and CPK elevation associated with daptomycin were morbidly obese based on their experience with high-dose daptomycin therapy [14]. Another study documented a CPK elevation (>1000 units/L) rate of 10.5% in morbidly-obese patients receiving a mean (standard deviation) daptomycin dose of 5.83 (1.14) mg/kg that matches our model-based predictions of 10.8% in this population [15]. Importantly, a dose-response relationship is evident from their analyses and corroborated by our exposure-response predictions [15].

Second, given that CL and V_c were nearly identical between groups, our findings indicate there may be an opportunity for administering daptomycin as a fixed, non-weight-based dose for morbidly-obese subjects. Although there is clearly an opportunity for fixed dosing, the daptomycin dose required to ensure a high probability of efficacy and low likelihood of toxicity remains unclear at this time until a dedicated fixed-dose study is conducted. The recent study of fixed televancin dosing for this weight-based approved drug confirms that some drugs currently dosed on TBW do not need to be dosed this way and can have an improvement in their safety margin with a shift in this dosing paradigm [16].

Although our findings regarding fixed dosing of daptomycin in morbidly-obese individuals clearly challenge a clinical paradigm, more PK/PD and clinical data are needed before altering clinical practice. Whereas our investigation had good internal validity, it only included female subjects who were relatively healthy with good kidney function. This limits our ability to generalize dosing to individuals with abnormal kidney function. The PK of daptomycin may be altered in infected patients so confirmation of our findings in morbidly-obese infected patients would be reasonable.

In conclusion, administration of a once-daily daptomycin 6 mg/kg dosage yields $AUC_{0\text{-}24SS}$, C_{maxss}, and C_{minss} values approximately two times higher in the morbidly-obese compared to non-obese individuals. In contrast, a fixed dosage once-daily regimen results in isometric exposures in both groups. Our findings suggest that use of daptomycin as a fixed, non-weight-based dose is more likely to result in bioequivalent exposures in morbidly-obese and non-obese adults. **Tables and Figures**

Legend

Table 1. Comparison of derived pharmacokinetic and population pharmacokinetic mean and standard deviation parameters between morbidly-obese and non-obese subjects. **Legend:** $^{=}V_c$ = apparent volume of distribution of the central compartment (liters); $^{=}CL$ =clearance (liters/hour); $^{=}K_{cp}$ = transfer rate constant from the central compartment to the peripheral compartment (per hour); $^{=}K_{pc}$ = transfer rate constant from the peripheral compartment to the central compartment (per hour); V_{ss} = apparent volume of distribution at steady state; $t_{1/2}$ = terminal plasma half-life (hour).

Table 2. Mean (standard deviation) pharmacokinetic parameters in morbidly-obese and non-obese subjects from a 9999-subject Monte Carlo simulation. **Legend:** $AUC_{0\text{-}24SS}$ = simulated area under the concentration-time curve; C_{maxss} = simulated maximum plasma concentration 0.5 hr after the end of infusion; C_{minss} = simulated minimum plasma concentration.

Figure 1. Relationship between individual Bayesian estimates of daptomycin A) V_c = apparent volume of distribution of the central compartment (liters) and B) CL = clearance (liters/hour) with Total Body Weight (TBW). **References**

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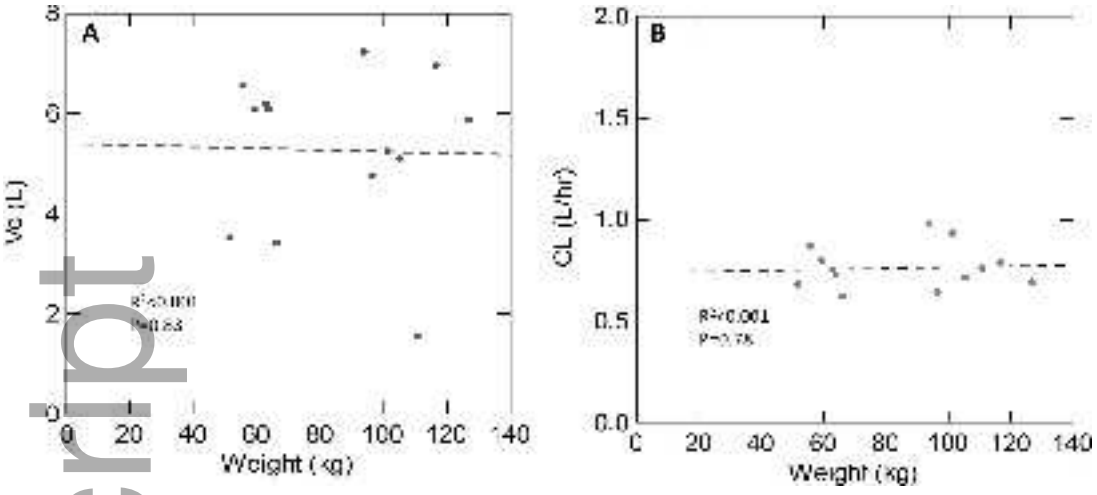
Table 1.

Pharmacokinetic parameters	Morbidly obese	Non-obese	*P*value
Population estimates			
V_c	5.13 ± 1.63	5.57 ± 1.39	0.48
CL	0.82 ± 0.19	0.77 ± 0.11	0.85
K_{cp}	0.88 ± 0.59	0.34 ± 0.34	0.03
K_{pc}	0.89 ± 0.41	0.51 ± 0.22	0.04
Derived estimates			
V_{ss}	9.44 ± 1.99	8.46 ± 1.49	0.66
$t_{1/2}$	8.16 ± 1.77	7.59 ± 0.63	0.75

Table 2.

Pharmacokinetic Parameters	Total body weight-based dosing (6 mg/kg/day)		Fixed dosing (500 mg/day)	
	Morbidly obese	Non-obese	Morbidly obese	Non-obese
$AUC_{0\text{-}24SS}$	877 (236)	511 (130)	638 (144)	658 (94)
C_{maxss}	97.1 (30.1)	55.4 (12.8)	70.8 (19.4)	78.5 (16.1)
C_{minss}	13.1 (8.7)	6.8 (4.1)	9.6 (6.1)	8.7 (4.7)



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