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Effect of Obesity on the Population Pharmacokinetics of Meropenem in Critically Ill Patients

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Severe pathophysiological changes in critical illness can lead to dramatically altered antimicrobial pharmacokinetics (PK). The additional effect of obesity on PK potentially increases the challenge for effective dosing. The aim of this prospective study was to describe the population PK of meropenem for a cohort of critically ill patients, including obese and morbidly obese patients. Critically ill patients prescribed meropenem were recruited into the following three body mass index (BMI) groups: nonobese (18.5 to 29.9 kg/m^2), obese (30.0 to 39.9 kg/m^2), and morbidly obese (≥40 kg/m^2). Serial plasma samples were taken, and meropenem concentrations were determined using a validated chromatographic method. Population PK analysis and Monte Carlo dosing simulations were undertaken with Pmetrics. Nineteen critically ill patients with different BMI categories were enrolled. The patients' mean ± standard deviation (SD) age, weight, and BMI were 49 ± 15.9 years, 95 ± 22.0 kg, and 33 ± 7.0 kg/m^2, respectively. A two-compartment model described the data adequately. The mean ± SD parameter estimates for the final covariate model were as follows: clearance (CL), 15.5 ± 6.0 liters/h; volume of distribution in the central compartment (V_1), 11.7 ± 5.8 liters; intercompartmental clearance from the central compartment to the peripheral compartment, 25.6 ± 35.1 liters h^{-1}; and intercompartmental clearance from the peripheral compartment to the central compartment, 8.32 ± 12.24 liters h^{-1}. Higher creatinine clearance (CL_{CR}) was associated with a lower probability of target attainment, with BMI having little effect. Although obesity was found to be associated with an increased V_1, dose adjustment based on CL_{CR} appears to be more important than patient BMI.

The prevalence of obesity worldwide has continued to escalate during recent decades (1, 2). According to data from different organizations, more than two-thirds of adults in the United States are overweight or obese, and more than one-third are obese (3, 4). Obesity is thought to be a risk factor for mortality and morbidity from different types of infection in the intensive care unit (ICU), as shown for various types of surgical site infections (e.g., after hysterectomy [5] or spinal surgery [6]), community-acquired pneumonia (7), and peritonitis in peritoneal dialysis patients (8). Optimized drug dosing is likely to reduce the burden associated with infections in these patients, although there are only sparse data available for clinicians to guide antimicrobial dosing in obese patients.

Dosing in obese critically ill patients is considered highly challenging (9, 10). Indeed, the pathophysiological changes associated with both obesity and critical illness may have additive effects on altered pharmacokinetics (PK), although there are very limited published data on this topic (11, 12). The physiological differences in obese patients include changes in regional blood flow, increased cardiac output, and increased fat and lean mass (13). These changes may alter PK and PK/pharmacodynamics (PK/PD) of antimicrobials, necessitating dosing adjustment. As the prevalence of obesity increases, clinicians more frequently confront the dosing challenges in treating these patients.

Meropenem is a broad-spectrum antimicrobial of the carbapenem class which is frequently used as empirical or directed therapy in critically ill patients (14). Meropenem shows time-dependent antibacterial activity. To date, the PK data for meropenem have not been well described for critically ill obese patients. *In vitro* and animal infection model data suggest that maintaining unbound concentrations above the MIC for 40% of the dosing interval under steady-state PK conditions should be considered a minimum exposure target (40% T_{MIC}). It remains unclear whether standard meropenem dosing regimens achieve this target in critically ill obese patients.

The aim of this prospective study was to describe the population PK of meropenem for a cohort of critically ill patients, including obese and morbidly obese patients.

MATERIALS AND METHODS

Setting. This was an observational PK study using one-interval patient sampling at a tertiary referral ICU. Ethics approval was obtained from the local institutional Human Research Ethics Committee (approval no. HRC/14/QRBW/88). Written informed consent was obtained from all participants or from their substitute decision-makers.

Study population. The inclusion criteria for this study were as follows: (i) age of ≥18 years, (ii) receiving meropenem (prophylaxis or treatment), and (iii) body mass index (BMI) of ≥18.5 kg/m^2. The exclusion criteria were as follows: (i) patients on renal replacement therapy, (ii)

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TABLE 1 Demographic and clinical data for patients in this study

Variable[a]	Mean value (SD)[b]				*P* value
	All patients ($n = 19$)	Nonobese patients ($n = 6$)	Obese patients ($n = 7$)	Morbidly obese patients ($n = 6$)	
Age (yr)	49 (15.9)	41 (19.1)	49 (16.2)	58 (7.6)	0.20
Weight (kg)	95 (22.0)	71 (11.6)	103 (6.8)	109 (23.3)	<0.01
Ideal body weight (kg)	65 (12.9)	65 (6.7)	72 (6.3)	55 (17.8)	0.05
Lean body weight (kg)	60 (13.1)	53 (7.3)	70 (4.7)	55 (17.7)	0.03
Height (cm)	171 (12.2)	173 (6.0)	177 (7.0)	162 (17.0)	0.07
Sex (male)	11 (58)	2 (33)	7 (100)	2 (33)	
BMI (kg/m^2)	33 (7.0)	24 (3.4)	33 (2.2)	41 (1.4)	<0.01
Scr (μmol/liter)	72 (24.0)	62 (26)	89 (20.2)	62 (16.2)	0.05
CG-TBW (ml/min)	151 (62.6)	139 (44.9)	114 (39.3)	206 (66.7)	0.02
CG-IBW (ml/min)	100 (47.5)	135 (59.9)	80 (30.3)	87 (34.2)	0.07
CG-LBW (ml/min)	89 (33.5)	107 (40.9)	77 (27.9)	86 (29.2)	0.29
Albumin level (g/liter)	26 (6.1)	24 (8.1)	28 (5.1)	24 (4.8)	0.40
SOFA score	6 (3.9)	5 (2.8)	6 (4.9)	6 (3.8)	0.80
APACHE II score	20 (6.9)	26 (3.7)	15 (4.2)	20 (6.9)	<0.01

[a] APACHE II, acute physiology and chronic health evaluation; BMI, body mass index; CL_{CR}, measured creatinine clearance; CG-TBW, estimated CL_{CR} calculated using Cockcroft-Gault equation based on total body weight; CG-IBW, estimated CL_{CR} calculated using Cockcroft-Gault equation based on ideal body weight; CG-LBW, estimated CL_{CR} calculated using Cockcroft-Gault equation based on lean body weight; Scr, serum creatinine; SOFA, sequential organ failure assessment.
[b] Data on male gender are presented as numbers (%) of patients.

pregnant women, (iii) actively bleeding patients, and (iv) patients with HIV or hepatitis.

Study protocol. Meropenem was administered according to the intensivist's decision, with dosage regimens of 500 mg, 1 g, and 2 g. Participants were categorized into the following three groups according to BMI: nonobese (BMI = 18.5 to 29.9 kg/m^2), obese (BMI = 30 to 39.9 kg/m^2), and morbidly obese (BMI of ≥40 kg/m^2). On a single occasion (one dosing interval), six blood samples were taken from each participant to determine plasma meropenem concentrations. Blood samples (about 3 ml) were drawn from the participants at the following times: predose and 30 min (end of infusion), 45 min, 1 h, 4 h, and 8 h after dose administration. Other clinical and demographic data were collected on the day of plasma sampling, including age, sex, weight, height, and BMI. Clinical data were also recorded, including SOFA and APACHE II scores, plasma albumin levels, and serum creatinine concentrations (Scr).

Sample handling, storage, and assay. Collected blood samples were placed immediately in an ice bath and were centrifuged at 3,000 rpm for 10 min. Plasma samples were stored at −80°C until bioanalysis. Meropenem concentrations in plasma were determined by validated high-performance liquid chromatography with UV detection (HPLC-UV) on a Shimadzu Prominence instrument. Sample analysis was conducted in batches, with calibration standards and quality controls to which batch acceptance criteria were applied. Acetonitrile was added to a 100-μl aliquot of plasma combined with an internal standard (cefotaxime) to precipitate proteins. Following centrifugation, the supernatant was isolated and washed with dichloromethane to remove acetonitrile and lipophilic components. Following centrifugation, the upper layer was isolated for chromatographic analysis. The stationary phase was a Waters XBridge C_{18} 2.1-mm by 50-mm column. The mobile phase was 4% acetonitrile-96% 50 mM phosphate buffer at pH 2.5 delivered isocratically. The eluent was monitored at 304 nm.

The calibration curve was linear, with a weighing of $1/x^2$ over the range of 0.2 to 100 μg/ml. The precision and accuracy at the lower limit of quantification (LLOQ) were ≤5.9%. The assay was validated against matrix effects (precision and accuracy within 4% at high and low concentrations). The assay's precision and accuracy were determined for both within-day and between-day comparisons and were within 6.5% at all three concentrations tested. Bioanalysis techniques were validated and conducted in accordance with the criteria of the U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (15).

Population pharmacokinetic modeling. The plasma meropenem concentrations were fitted to one- and two-compartment models by using a nonparametric adaptive grid (NPAG) algorithm within the Pmetrics package for R (Laboratory of Applied Pharmacokinetics and Bioinformatics, Los Angeles, CA) (16, 17). Clearance (CL) from the central compartment and intercompartmental distribution were modeled as first-order processes.

Demographic and clinical characteristics that were considered biologically plausible for affecting meropenem PK were tested for inclusion as covariates. Age, total body weight (TBW), ideal body weight (IBW), lean body weight (LBW), sex, BMI, BMI category, Scr, creatinine clearance (CL_{CR}) (estimated by the Cockcroft-Gault equation by separately using TBW, LBW, and IBW), albumin level, SOFA score, and APACHE II score were tested. Each of these covariates was plotted against the PK parameter estimates to assess the level of correlation. Covariates were retained in the model if they showed a significant improvement in the log likelihood ($P < 0.05$) and/or improved the goodness-of-fit plots.

Model diagnostics. A visual prediction check (VPC) of the observed-predicted concentration scatterplot, the coefficient of determination of linear regression of observed-predicted values, and the log likelihood values for each run were used to evaluate the goodness of fit. Predictive performance evaluation was based on the means for both prediction error (bias) and bias-adjusted squared prediction error (imprecision) for the population and individual prediction models for the central compartment.

PTA. Monte Carlo simulations ($n = 1{,}000$) were performed using Pmetrics software to determine the probability of target attainment (PTA) with a variety of MICs for CL_{CR} values and BMI classes. Meropenem doses of 500 mg given intravenously (i.v.) every 8 h (q8h) as intermittent 30-min or 3-h prolonged infusions, 1,000 mg given i.v. q8h as intermittent or prolonged infusions, and 2,000 mg given i.v. q8h as intermittent or prolonged infusions were simulated at three different levels of renal function (CL_{CR} = 30, 50, and 150 ml/min) and for three BMI categories (nonobese, obese, and morbidly obese). The PTA for achieving 40% T_{MIC} (meropenem plasma concentration remains above the MIC for at least 40% of the dosing interval) was calculated for the first 24 h of therapy (3 doses given q8h). Unbound concentrations were calculated using previously published data on the free fraction of meropenem (98%) (18).

FTA calculation. MIC data for pathogens that are commonly targeted for treatment with meropenem, i.e., *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, were obtained from the European Committee for

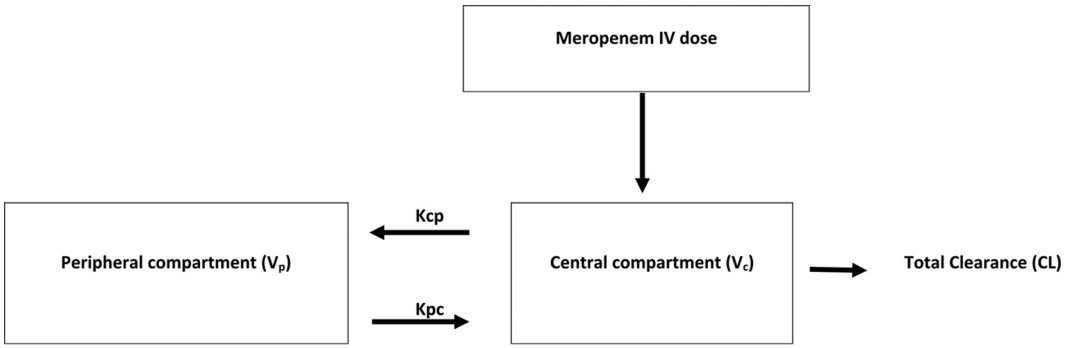

FIG 1 Structural PK model for meropenem in critically ill obese and nonobese patients. The model contains the volumes of distribution for the central compartment (plasma; V_c) and the peripheral compartment (V_p), a rate constant for meropenem distribution from the central to the peripheral compartment (Kcp), and a rate constant for meropenem distribution from the peripheral to the central compartment (Kpc).

Antimicrobial Susceptibility and Testing (EUCAST) database (www.eucast.org) to determine the fractional target attainment (FTA). The FTA describes the pharmacodynamic exposure (PTA) of meropenem against a MIC distribution. The FTA threshold was achieved when the value exceeded 90%. Susceptible MIC distributions for both pathogens (MICs of ≤2 mg/liter) were used to determine the FTA for directed therapy. Additionally, we determined the FTA for the entire MIC distribution (including values for susceptible and resistant isolates) to describe dosing during empirical therapy.

Statistical analysis. Continuous variables are presented as means (standard deviations [SD]) or medians (interquartile ranges), as appropriate. Categorical variables are expressed as absolute numbers and relative frequencies. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for normality. One-way analysis of variance (ANOVA) was used to test for differences in demographic and clinical data between the BMI categories. Linear regression was used to describe correlations between patient weight metrics in the 3 BMI categories and the volume of distribution in the central compartment (V_1) and CL values for meropenem. All statistical analyses were performed using the statistical software package IBM-SPSS Statistics 22.0 (IBM, New York, NY). *P* values of <0.05 were considered statistically significant.

RESULTS

Demographic and clinical data. Nineteen critically ill patients (11 males) were enrolled in the study, including seven nonobese, six obese, and six morbidly obese patients. In total, 112 plasma samples were obtained from these patients. The demographic and clinical data for the respective BMI categorizations are shown in Table 1. Only patients' weights, BMIs, and APACHE II scores were significantly different between the three BMI categorizations ($P < 0.05$).

Pharmacokinetic model building. The meropenem PK was best described by a two-compartment linear model with zero-order input of drug into the central compartment (Fig. 1). Regarding covariates, the Cockcroft-Gault CL_{CR} (CG-CL_{CR}) was tested, with CG-CL_{CR} calculated using TBW, LBW, and IBW separately. The CG-CL_{CR} calculated using TBW (normalized to 100 ml/min) for meropenem CL improved the model fit best. For the meropenem volume of distribution in the central compartment (V_1), we applied two categories of BMI (above and below 35 kg/m^2), as this resulted in a more significant improvement in the model than using one or three categories. Furthermore, a scaling factor for the effect of obesity (O) on V_1 in the group with BMIs of >35 kg/m^2 was included. When these covariates were added, each resulted in a statistically significant improvement in the log likelihood from the previous model ($P < 0.01$). The final model was as follows:

$$\mathrm{TVCL} = \mathrm{CL} \times \mathrm{CG\text{-}CL_{CR}}/100 \quad (1)$$

$$\mathrm{TV}V_1 = V_1 \times (\mathrm{BMI}/30)^{0.75} \ (\text{if BMI is} < 35\ \mathrm{kg/m^2}) \quad (2)$$

$$\mathrm{TV}V_1 = V_C \times (\mathrm{BMI}/38)^{0.75} \times \mathrm{O} \ (\text{if BMI is} > 35\ \mathrm{kg/m^2}) \quad (3)$$

where CG-CL_{CR} is the estimated CL_{CR} calculated using the Cockcroft-Gault equation, TVCL is the typical value for meropenem clearance, CL is the population parameter estimate for meropenem clearance, TVV_1 is the typical value for the meropenem volume of distribution in the central compartment, V_1 is the population parameter estimate for the volume of the central compartment, and O is a scaling factor for obesity.

The mean ± SD population pharmacokinetic parameter estimates from the final covariate model are shown in Table 2. The diagnostic plots to confirm the goodness of fit of the model were considered acceptable and are shown in Fig. 2. The final covariate model was then used for Monte Carlo dosing simulations.

Figure 3 shows the observed relationships between V_1 and CL and the mean body weights for the three BMI categories. None of the measured correlations were statistically significant, although as described in our model building process, the inclusion of the effect of BMI on V_1 improved the goodness-of-fit plots of the model.

Dosing simulations. Monte Carlo simulations and PTA for achieving 40% T_{MIC} for various meropenem doses are presented

TABLE 2 Parameter estimates for meropenem obtained from the final covariate two-compartment population pharmacokinetic model

Parameter[a]	Mean (SD)	Coefficient of variation (%)	Median
CL (liters/h)	15.50 (5.99)	38.8	14.3
V_1 (liters)	11.66 (5.75)	49.3	11.1
k_{CP} (h^{-1})	25.60 (35.14)	137.2	5.2
k_{PC} (h^{-1})	8.32 (12.24)	147.1	3.9
O	1.43 (0.46)	32.0	1.5

[a] CL, population clearance of meropenem; V_1, population volume of distribution in the central compartment; k_{CP}, rate constant for meropenem distribution from the central to the peripheral compartment; k_{PC}, rate constant for meropenem distribution from the peripheral to the central compartment; O, scaling factor for obesity.

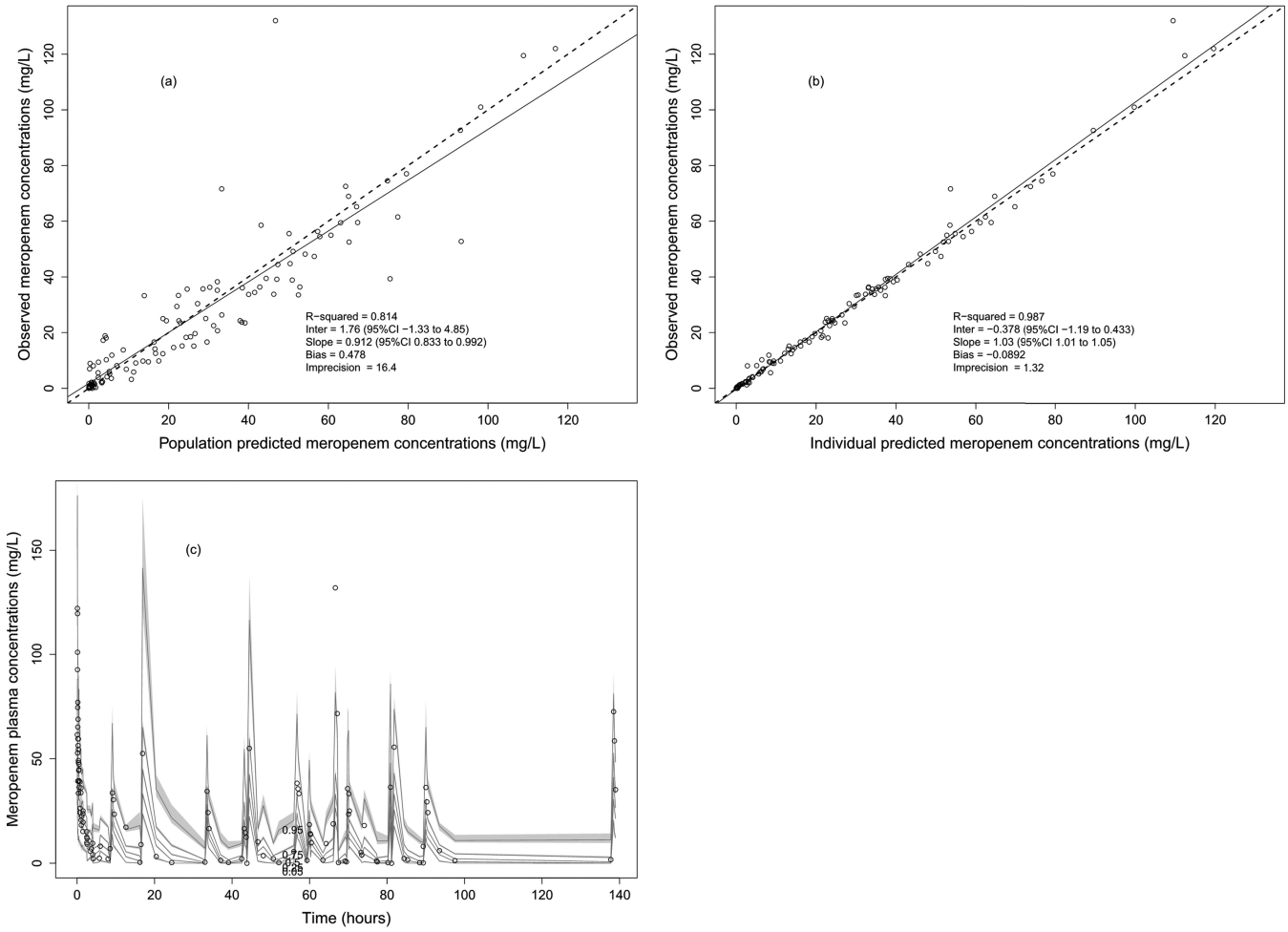

FIG 2 Diagnostic plots for the final population pharmacokinetic covariate model. (a) Observed meropenem concentrations versus population predicted meropenem concentrations ($R^2 = 0.814$). (b) Observed meropenem concentrations versus individual predicted meropenem concentrations ($R^2 = 0.987$). (c) Visual predictive check.

in Table 3. The results showed that increasing CL_{CR} was associated with a lower PTA for different BMI categories. Furthermore, at the high CL_{CR} of 150 ml/min, the intermittent dosing regimens of 500 mg and 1,000 mg consistently failed to achieve the PK/PD target for a MIC of 2 mg/liter in almost all BMI groups. In contrast, all prolonged-infusion doses as well as intermittent infusions of 2,000 mg achieved PK/PD targets up to a MIC of at least 2 mg/liter.

Fractional target attainment. The FTA values for different simulated dosing regimens and patient BMIs and CL_{CR} for both directed and empirical coverage of *A. baumannii* and *P. aeruginosa*

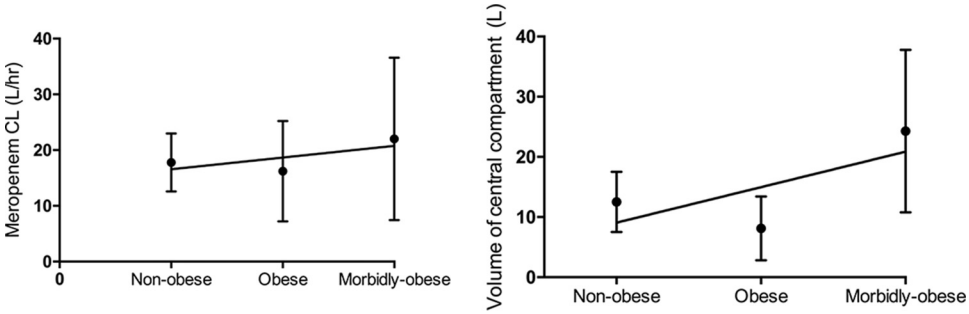

FIG 3 (Left) Relationship of meropenem clearance to the mean (SD) body weights for the BMI categorizations (for clearance versus BMI linear regression, $r^2 = 0.4915$). (Right) Relationship of volume of distribution of the central compartment (V_1) to the mean (SD) body weights for the prespecified BMI categorizations (nonobese, obese, and morbidly obese) (for V_1 versus BMI linear regression, $r^2 = 0.4961$).

TABLE 3 Meropenem probabilities of target attainment for different BMI groups, CL_{CR} values, and dosage regimens and methods of administration[a]

Dose (mg) q8h (infusion interval)	BMI group	CL_{CR} (ml/min)	Attainment of PTA for MIC (mg/liter)					
			0.5	1	2	4	8	16
500 (II)	Nonobese	30	+	+	+	+	−	−
		50	+	+	+	+	−	−
		150	−	−	−	−	−	−
	Obese	30	+	+	+	+	−	−
		50	+	+	+	+	−	−
		150	−	−	−	−	−	−
	Morbidly obese	30	+	+	+	+	−	−
		50	+	+	+	+	−	−
		150	+	−	−	−	−	−
500 (PI)	Nonobese	30	+	+	+	+	−	−
		50	+	+	+	+	−	−
		150	+	+	+	−	−	−
	Obese	30	+	+	+	+	−	−
		50	+	+	+	+	−	−
		150	+	+	+	−	−	−
	Morbidly obese	30	+	+	+	+	−	−
		50	+	+	+	+	−	−
		150	+	+	+	−	−	−
1,000 (II)	Nonobese	30	+	+	+	+	+	−
		50	+	+	+	+	+	−
		150	−	−	−	−	−	−
	Obese	30	+	+	+	+	+	−
		50	+	+	+	+	+	−
		150	+	−	−	−	−	−
	Morbidly obese	30	+	+	+	+	+	−
		50	+	+	+	+	+	−
		150	+	+	−	−	−	−
1,000 (PI)	Nonobese	30	+	+	+	+	+	−
		50	+	+	+	+	+	−
		150	+	+	+	+	−	−
	Obese	30	+	+	+	+	+	−
		50	+	+	+	+	+	−
		150	+	+	+	+	−	−
	Morbidly obese	30	+	+	+	+	+	−
		50	+	+	+	+	+	−
		150	+	+	+	+	−	−
2,000 (II)	Nonobese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	−	−	−	−	−
	Obese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	+	−	−	−	−
	Morbidly obese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	+	+	−	−	−
2,000 (PI)	Nonobese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	+	+	+	+	−
	Obese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	+	+	+	+	−
	Morbidly obese	30	+	+	+	+	+	+
		50	+	+	+	+	+	+
		150	+	+	+	+	+	−

[a] The target was for the drug concentration to remain above the MIC for 40% of the dosage interval to achieve bactericidal activity. The meropenem target MIC was chosen according to the EUCAST breakpoint (2 mg/liter). BMI, body mass index; q8h, three-times-daily dosing; CL_{CR}, creatinine clearance; II, intermittent infusion; IP, prolonged infusion.

are shown in Table 4. For empirical therapy, meropenem at 500 mg q8h as intermittent or prolonged infusions failed to achieve 90% coverage of *A. baumannii* in all BMI groups at different CL_{CR} levels. However, as CL_{CR} increased (i.e., CL_{CR} of ≥50 ml/min), meropenem given at 500 mg q8h as intermittent or prolonged infusions also failed to achieve 90% coverage of *P. aeruginosa*. Using the higher meropenem dose of 2,000 mg q8h as prolonged infusions enabled coverage of ≥90% of *P. aeruginosa* organisms in all BMI groups at different CL_{CR} levels. However, this higher dose of meropenem failed to achieve 90% coverage of *A. baumannii* in obese and morbidly obese patients at CL_{CR} levels of 150 ml/min or greater.

For directed therapy, meropenem at 500 mg q8h as intermittent infusions failed to achieve 90% coverage of *A. baumannii* and *P. aeruginosa* when CL_{CR} was 150 ml/min or higher. Using meropenem at 500 mg q8h as prolonged infusions or use of an increased dose (i.e., 1,000 mg and 2,000 mg) enabled coverage of ≥90% of *A. baumannii* and *P. aeruginosa* organisms in all BMI groups at different CL_{CR} levels.

DISCUSSION

To the best our knowledge, this is the first prospective population PK study of meropenem in morbidly obese, obese, and nonobese critically ill patients. We found that BMI was a significant covariate describing meropenem V_1, but when BMI was included in dosing simulations, the presence of different BMIs did not greatly affect PK/PD target attainment. Importantly, we observed that a higher CL_{CR} (≥150 ml/min) was associated with a lower achievement of PK/PD targets for all patients, while a standard dosing regimen achieved PK/PD targets for patients with low and normal kidney function.

As with antibiotic studies, the susceptibility of the pathogen is of paramount importance to effective drug therapy. In this case, we evaluated the fractional target attainment against *A. baumannii* and *P. aeruginosa* with susceptible MIC distributions that are encountered as part of directed therapy. We found for almost all dosing scenarios that meropenem achieved PK/PD targets successfully, with the exception of lower doses in the presence of high CL_{CR} (>150 ml/min). This suggests that when meropenem is used for directed therapy against pathogens with MICs of <2 mg/liter,

TABLE 4 Fractional target attainment for various meropenem dosing regimens, CL_{CR} values, and BMI groups[a]

Dose (mg) q8h (infusion interval)	BMI group	CL_{CR} (ml/min)	FTA (%)			
			Acinetobacter baumannii		*Pseudomonas aeruginosa*	
			MIC for directed therapy	MIC for empirical therapy	MIC for directed therapy	MIC for empirical therapy
500 (II)	Nonobese	30	98.93	86.22	99.02	90.92
		50	97.86	81.64	98.06	86.44
		150	74.31	57.03	77.91	62.90
	Obese	30	99.15	85.62	99.25	90.52
		50	98.38	81.75	98.54	86.57
		150	82.14	62.98	85.20	68.75
	Morbidly obese	30	99.34	84.70	99.44	89.58
		50	98.69	81.67	98.88	86.46
		150	87.65	67.14	90.06	72.61
500 (PI)	Nonobese	30	99.93	87.66	99.95	92.29
		50	99.89	84.40	99.92	89.28
		150	99.61	77.69	99.73	81.98
	Obese	30	99.83	86.51	99.87	91.34
		50	99.81	83.53	99.86	88.38
		150	99.25	76.94	99.48	81.27
	Morbidly obese	30	99.72	85.22	99.81	90.03
		50	99.67	82.79	99.77	87.58
		150	98.60	76.14	99.06	80.57
1,000 (II)	Nonobese	30	99.19	94.33	99.24	96.62
		50	98.38	88.62	98.49	92.48
		150	84.58	67.19	86.56	72.37
	Obese	30	99.43	94.12	99.48	96.55
		50	99.67	91.84	99.72	95.07
		150	90.77	72.44	91.99	77.36
	Morbidly obese	30	99.63	92.65	99.67	95.61
		50	99.23	88.19	99.32	92.48
		150	94.49	75.81	95.18	80.54
1,000 (PI)	Nonobese	30	99.98	95.72	99.99	97.82
		50	99.97	91.86	99.98	95.29
		150	99.97	83.51	99.98	88.28
	Obese	30	99.94	94.92	99.96	97.26
		50	99.94	90.56	99.96	94.39
		150	99.93	82.97	99.95	87.71
	Morbidly obese	30	99.95	92.99	99.97	95.94
		50	99.95	89.38	99.97	93.52
		150	99.91	82.44	99.94	87.14
2,000 (II)	Nonobese	30	99.33	96.62	99.38	98.18
		50	98.68	94.80	98.75	96.75
		150	90.15	75.28	91.19	80.01
	Obese	30	99.58	96.75	99.61	98.33
		50	99.04	95.27	99.10	97.20
		150	94.19	79.69	94.76	84.29
	Morbidly obese	30	99.75	96.62	99.77	98.31
		50	99.47	95.46	99.52	97.45
		150	96.38	82.37	96.72	87.02
2,000 (PI)	Nonobese	30	100.00	97.52	100.00	98.99
		50	100.00	97.09	100.00	98.73
		150	100.00	90.09	100.00	94.14
	Obese	30	100.00	97.81	100.00	99.45
		50	100.00	97.27	100.00	99.11
		150	100.00	89.60	100.00	93.86
	Morbidly obese	30	100.00	97.41	100.00	99.17
		50	100.00	96.79	100.00	98.77
		150	100.00	88.84	100.00	93.23

[a] BMI, body mass index; CL_{CR}, creatinine clearance; II, intermittent infusion; PI, prolonged infusion.

dose adjustment is rarely necessary. However, when meropenem is used as part of empirical therapy before the susceptibilities of the pathogens are known, depending on local susceptibility patterns in the case of possible *A. baumannii* or *P. aeruginosa* infection, higher doses and/or use of prolonged infusion should be considered until the pathogen and susceptibility have been characterized.

At higher CL_{CR} levels (≥150 ml/min) in critically ill patients in all BMI groups, intermittent meropenem dosing regimens consistently failed to achieve PK/PD targets. This failure could be remedied by adjusting either the dose or the duration of infusion. Specifically, meropenem at 500 mg or 1,000 mg q8h did not achieve the PK/PD target for the EUCAST breakpoint for *A. baumannii* and *P. aeruginosa* of a MIC of 2 mg/liter. When the doses were escalated to 2,000 mg q8h, the PK/PD target was achieved. Similarly, when meropenem was administered as a prolonged infusion (3 h), PK/PD target achievement increased significantly, even for lower doses of 500 mg q8h. This finding is not new for use of meropenem in critically ill patients, but it is novel in the context of the range of BMIs investigated in this study.

Of all the patient characteristics tested in this study, CL_{CR} had by far the greatest influence on achievement of PK/PD targets for meropenem. Even increasing BMI, which has been proposed to likely be associated with reduced meropenem PK exposures, had a far smaller overall effect than CL_{CR}. The BMI effect was described in our model as being associated with changes in the V_1, which may indicate that altered concentrations are most likely in early dosing intervals but will be irrelevant thereafter, when dosing should be performed based only on CL_{CR}. Interestingly, as shown in Fig. 3, BMI was not well correlated with meropenem CL or V_1. Other weight descriptors were also not correlated, highlighting the variable effect that increasing body weight has on meropenem PK.

A recent retrospective study of 1,400 patients evaluated the effect of obesity on the unbound plasma concentrations of piperacillin and meropenem (19). For meropenem, the presence of obesity did not significantly affect unbound concentrations. The authors of that study used logistic regression to demonstrate that dosing based on CL_{CR} was the strongest predictor of therapeutic concentrations in critically ill patients, including the obese (odds ratio [OR], 21.74; 95% confidence interval [CI], 6.02 to 76.92). Another study retrospectively evaluated the PK of broad-spectrum β-lactam antibiotics, including meropenem, in critically ill obese and nonobese patients. That study analyzed routine therapeutic drug monitoring (TDM) data from 17 obese (BMI of ≥30 kg/m^2) and 17 nonobese (BMI of <25 kg/m^2) patients and found that meropenem CL values were not significantly different between the critically ill obese and nonobese patients (20). However, the total volume of distribution was nonsignificantly higher in the obese group (40.0 liters versus 27.9 liters; $P = 0.10$). The authors concluded that TDM should be performed routinely for obese critically ill patients.

In a small prospective PK study of 9 morbidly obese critically ill patients (mean ± SD BMI, 54.7 ± 8.6 kg/m^2), Cheatham et al. (21) also found that CL values for meropenem were similar between the enrolled morbidly obese patients and previously published data on nonobese patients. Like the present study and that of Hites et al. (20), the total volume of distribution (in that study described as the volume of distribution at steady state [V_{ss}]) was numerically larger in the morbidly obese group (37.8 liters versus 21.7 liters). It was suggested that standard dosing regimens of meropenem can provided adequate PK/PD target attainment for susceptible pathogens (MICs of ≤2 mg/liter). The data from these previous studies generally support our results, with BMI, often described as an obesity category, affecting *V* but not CL and having little effect on achievement of PK/PD targets.

This analysis has some limitations. First, estimation of CL_{CR} by using the Cockcroft-Gault method is known to be suboptimal for critically ill patients. However, it is still commonly used clinically, although 8- or 24-h urinary CL_{CR} measurements should be used where possible for increased accuracy (22–24). Given that we did not have urinary CL_{CR} values, we used Cockcroft-Gault CL_{CR} values in our modeling process and found that they greatly improved the model, and thus they were retained. Notably, the weight descriptor for CG-CL_{CR} was TBW, and clinicians should use this weight metric in calculating CG-CL_{CR} for meropenem dosing. Second, although this is the largest prospective PK study of its type for meropenem, the sample size in this study is not sufficient for quantification of the effect of meropenem exposure on patient outcomes. Third, in the morbidly obese group ($n = 6$), the higher BMI was associated predominantly with a lower patient height rather than a higher weight. It is possible that a high BMI due to high weight may affect the PK of meropenem in a different way. Furthermore, increasing the sample size may also have helped to define additional patient factors associated with altered PK and to include a wider range of heights and weights, although these may not be clinically relevant.

Conclusions. In summary, this analysis presents the first population pharmacokinetic study of meropenem in critically ill patients with three different BMI categories. BMI appears to have a minimal effect on PK/PD target attainment in critically ill patients, while increasing CG-CL_{CR} (calculated using TBW) values were strongly associated with lower PK/PD target attainment rates. Higher doses or prolonged infusions should be applied for pathogens that have a higher MIC and/or for critically ill obese and nonobese patients with high CL_{CR} values. TDM of meropenem should be used where possible to help to optimize meropenem dosing regimens accordingly.

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REFERENCES

1. **Dixon JB.** 2015. The global burden of obesity and diabetes, p 1–6. *In* Brethauer SA, Schauer PR, Schirmer BD (ed), Minimally invasive bariatric surgery. Springer, New York, NY.
2. **Keating C, Backholer K, Gearon E, Stevenson C, Swinburn B, Moodie M, Carter R, Peeters A.** 2015. Prevalence of class-I, class-II and class-III

obesity in Australian adults between 1995 and 2011–12. Obes Res Clin Pract **9:**553–562. http://dx.doi.org/10.1016/j.orcp.2015.02.004.
3. **Weight-control Information Network.** 2012. Overweight and obesity statistics. U.S. Department of Health and Human Services, Weight-control Information Network, Bethesda, Maryland. http://www.niddk.nih.gov/health-information/health-statistics/Documents/stat904z.pdf.
4. **Fryar CD, Carroll MD, Ogden CL.** 2015. Prevalence of overweight, obesity, and extreme obesity among adults: United States, 1960–1962 through 2011–2012. CDC, Atlanta, GA. http://www.cdc.gov/nchs/data/hestat/obesity_adult_11_12/obesity_adult_11_12.htm.
5. **Löfgren M, Poromaa IS, Stjerndahl JH, Renström B.** 2004. Postoperative infections and antibiotic prophylaxis for hysterectomy in Sweden: a study by the Swedish National Register for Gynecologic Surgery. Acta Obstet Gynecol Scand **83:**1202–1207.
6. **Olsen MA, Mayfield J, Lauryssen C, Polish LB, Jones M, Vest J, Fraser VJ.** 2003. Risk factors for surgical site infection in spinal surgery. J Neurosurg Spine **98:**149–155. http://dx.doi.org/10.3171/spi.2003.98.2.0149.
7. **Baik I, Curhan GC, Rimm EB, Bendich A, Willett WC, Fawzi WW.** 2000. A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch Intern Med **160:**3082–3088. http://dx.doi.org/10.1001/archinte.160.20.3082.
8. **McDonald SP, Collins JF, Rumpsfeld M, Johnson DW.** 2004. Obesity is a risk factor for peritonitis in the Australian and New Zealand peritoneal dialysis patient populations. Perit Dial Int **24:**340–346.
9. **Lisboa T, Rello J, Richart C, Anzueto A, El Solh AA.** 2009. Obesity and critical care. Clin Pulm Med **16:**202–211. http://dx.doi.org/10.1097/CPM.0b013e3181ad2171.
10. **Alobaid AS, Hites M, Lipman J, Taccone FS, Roberts JA.** 2016. Effect of obesity on the pharmacokinetics of antimicrobials in critically ill patients: a structured review. Int J Antimicrob Agents **47:**259–268. http://dx.doi.org/10.1016/j.ijantimicag.2016.01.009.
11. **Pai MP, Bearden DT.** 2007. Antimicrobial dosing considerations in obese adult patients. Pharmacotherapy **27:**1081–1091. http://dx.doi.org/10.1592/phco.27.8.1081.
12. **Blot SI, Pea F, Lipman J.** 2014. The effect of pathophysiology on pharmacokinetics in the critically ill patient— concepts appraised by the example of antimicrobial agents. Adv Drug Deliv Rev **77:**3–11. http://dx.doi.org/10.1016/j.addr.2014.07.006.
13. **Jain R, Chung S, Jain L, Khurana M, Lau S, Lee J, Vaidyanathan J, Zadezensky I, Choe S, Sahajwalla C.** 2011. Implications of obesity for drug therapy: limitations and challenges. Clin Pharmacol Ther **90:**77–89. http://dx.doi.org/10.1038/clpt.2011.104.
14. **Baldwin CM, Lyseng-Williamson KA, Keam SJ.** 2008. Meropenem: a review of its use in the treatment of serious bacterial infections. Drugs **68:**803–838. http://dx.doi.org/10.2165/00003495-200868060-00006.
15. **Center for Drug Evaluation and Research.** 2001. Guidance for industry: bioanalytical method validation. Center for Drug Evaluation and Research, Rockville, MD. www.fda.gov/downloads/Drugs/Guidances/ucm070107.
16. **Tatarinova T, Neely M, Bartroff J, van Guilder M, Yamada W, Bayard D, Jelliffe R, Leary R, Chubatiuk A, Schumitzky A.** 2013. Two general methods for population pharmacokinetic modeling: non-parametric adaptive grid and non-parametric Bayesian. J Pharmacokinet Pharmacodyn **40:**189–199. http://dx.doi.org/10.1007/s10928-013-9302-8.
17. **Neely M, van Guilder M, Yamada W, Schumitzky A, Jelliffe R.** 2012. Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R. Ther Drug Monit **34:**467. http://dx.doi.org/10.1097/FTD.0b013e31825c4ba6.
18. **Craig WA.** 1997. The pharmacology of meropenem, a new carbapenem antibiotic. Clin Infect Dis **24:**S266–S275. http://dx.doi.org/10.1093/clinids/24.Supplement_2.S266.
19. **Alobaid AS, Brinkmann A, Frey OR, Roehr AC, Luque S, Grau S, Wong G, Abdul-Aziz MH, Roberts MS, Lipman J, Roberts JA.** 2016. What is the effect of obesity on piperacillin and meropenem trough concentrations in critically ill patients? J Antimicrob Chemother **71:**696–702. http://dx.doi.org/10.1093/jac/dkv412.
20. **Hites M, Taccone FS, Wolff F, Cotton F, Beumier M, De Backer D, Roisin S, Lorent S, Surin R, Seyler L, Vincent JL, Jacobs F.** 2013. Case-control study of drug monitoring of beta-lactams in obese critically ill patients. Antimicrob Agents Chemother **57:**708–715. http://dx.doi.org/10.1128/AAC.01083-12.
21. **Cheatham SC, Fleming MR, Healy DP, Chung EK, Shea KM, Humphrey ML, Kays MB.** 2014. Steady-state pharmacokinetics and pharmacodynamics of meropenem in morbidly obese patients hospitalized in an intensive care unit. J Clin Pharmacol **54:**324–330. http://dx.doi.org/10.1002/jcph.196.
22. **Grootaert V, Willems L, Debaveye Y, Meyfroidt G, Spriet I.** 2012. Augmented renal clearance in the critically ill: how to assess kidney function. Ann Pharmacother **46:**952–959. http://dx.doi.org/10.1345/aph.1Q708.
23. **Baptista JP, Udy AA, Sousa E, Pimentel J, Wang L, Roberts JA, Lipman J.** 2011. A comparison of estimates of glomerular filtration in critically ill patients with augmented renal clearance. Crit Care **15:**R139. http://dx.doi.org/10.1186/cc10262.
24. **Martin JH, Fay MF, Udy A, Roberts J, Kirkpatrick C, Ungerer J, Lipman J.** 2011. Pitfalls of using estimations of glomerular filtration rate in an intensive care population. Intern Med J **41:**537–543. http://dx.doi.org/10.1111/j.1445-5994.2009.02160.x.