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PHARMACOLOGY

Population Pharmacokinetics of Piperacillin in Nonobese, Obese, and Morbidly Obese Critically Ill Patients

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ABSTRACT The treatment of infections in critically ill obese and morbidly obese patients is challenging because of the combined physiological changes that result from obesity and critical illness. The aim of this study was to describe the population pharmacokinetics of piperacillin in a cohort of critically ill patients, including obese and morbidly obese patients. Critically ill patients who received piperacillin-tazobactam were classified according to their body mass index (BMI) as nonobese, obese, and morbidly obese. Plasma samples were collected, and piperacillin concentrations were determined by a validated chromatographic method. Population pharmacokinetic analysis and Monte Carlo dosing simulations were performed using Pmetrics software. Thirty-seven critically ill patients (including 12 obese patients and 12 morbidly obese patients) were enrolled. The patients' mean ± standard deviation age, weight, and BMI were 50 ± 15 years, 104 ± 35 kg, and 38.0 ± 15.0 kg/m^2, respectively. The concentration-time data were best described by a two-compartment linear model. The mean ± SD parameter estimates for the final covariate model were a clearance of 14.0 ± 7.1 liters/h, a volume of distribution of the central compartment of 49.0 ± 19.0 liters, an intercompartmental clearance from the central compartment to the peripheral compartment of 0.9 ± 0.6 liters · h^{-1}, and an intercompartmental clearance from the peripheral compartment to the central compartment of 2.3 ± 2.8 liters · h^{-1}. A higher measured creatinine clearance and shorter-duration infusions were associated with a lower likelihood of achieving therapeutic piperacillin exposures in patients in all BMI categories. Piperacillin pharmacokinetics are altered in the presence of obesity and critical illness. As with nonobese patients, prolonged infusions increase the likelihood of achieving therapeutic concentrations.

KEYWORDS antibiotics, creatinine clearance, dosing, morbid obesity, pharmacodynamics, pharmacokinetics

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In recent decades, obesity has increased in prevalence globally (1, 2). Similar to other western countries, in the United States, more than two-thirds of adults are either overweight or obese (3, 4). Critically ill obese patients are thought to be at a higher risk

TABLE 1 Demographic and clinical data[a]

Variable	Values for the following: All patients (n = 37)	Nonobese patients (n = 13)	Obese patients (n = 12)	Morbidly obese patients (n = 12)	P value
Age (yr)	50 (15)	48 (17)	47 (12)	54 (16)	0.46
Wt (kg)	104 (35)	81 (11)	90 (10)	143 (34)	<0.001
IBW (kg)	61 (13)	68 (9)	60 (11)	55 (16)	0.029
LBW (kg)	52 (23)	60 (6)	58 (10)	38 (10)	0.30
Ht (cm)	167 (12)	173 (9)	167 (10)	161 (15)	0.46
Male sex[b]	21 (57)	11 (84)	6 (50)	4 (33)	
BMI (kg/m^2)	38 (15)	27 (3)	33 (2)	55 (14)	<0.001
Serum creatinine concn (μmol/liter)	95 (53)	87 (31)	76 (28)	124 (78)	0.66
Measured CL_{CR} (ml/min)	108 (59)	123 (59)	113 (45)	86 (68)	0.26
CG-TBW (ml/min)	165 (86)	135 (68)	173 (60)	191 (116)	0.25
CG-IBW (ml/min)	103 (58)	117 (66)	114 (40)	77 (58)	0.16
CG-LBW (ml/min)	90 (57)	102 (54)	108 (34)	58 (68)	0.06
SOFA score	6 (3)	7 (3)	7 (4)	4 (4)	0.07
APACHE II score	21 (7)	21 (7)	21 (7)	21 (7)	0.97

[a]Data for each BMI category are presented in a separate column. Data represent means (SDs) unless indicated otherwise. APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CG-TBW, CL_{CR} estimated using the Cockcroft-Gault equation based on total body weight; CG-IBW, CL_{CR} estimated using the Cockcroft-Gault equation based on ideal body weight; CG-LBW, CL_{CR} estimated using the Cockcroft-Gault equation based on lean body weight; CL_{CR}, creatinine clearance; SOFA, Sequential Organ Failure Assessment.

[b]Data for male sex are presented as the number (percent) of subjects.

of mortality and morbidity from serious infections, including surgical site infections and community-acquired pneumonia, than nonobese patients (5–8). The optimization of antimicrobial doses should be considered crucial in order to maximize the success of treatment in these patients, although only sparse data are available to guide dosing (9, 10). Indeed, obesity is thought to augment the pathophysiological changes that occur due to critical illness, which may lead to additional changes in antimicrobial pharmacokinetics (PK) (11, 12). The chronic physiological changes associated with obesity itself include reduced regional blood flow, increased cardiac output, and increased adipose tissue mass as well as increased lean mass, all of which may affect antimicrobial PK/pharmacodynamics (PD) (13).

Piperacillin is a β-lactam antibiotic with bactericidal activity against a broad spectrum of Gram-negative and Gram-positive aerobes and anaerobes (14). It is commonly coformulated with tazobactam (a β-lactamase inhibitor) to enhance its activity against β-lactamase-producing pathogens (15, 16). Piperacillin exhibits time-dependent bacterial killing, meaning that efficacy is determined by the duration that free concentrations are maintained above the MIC (fT_{MIC}) for the pathogens (17). For piperacillin, an fT_{MIC} of ≥50% of the dosing interval is considered necessary for maximal activity (18).

There are few data on the PK of piperacillin in obese patients, particularly critically ill obese patients. Therefore, it remains unclear whether standard piperacillin dosing regimens will provide sufficient drug exposure. The aim of this prospective study was to describe the population PK of piperacillin in a cohort of critically ill nonobese, obese, and morbidly obese patients. We then sought to perform Monte Carlo dosing simulations to identify optimized dosing regimens suitable for critically ill obese and morbidly obese patients.

RESULTS

Demographic and clinical data. Thirty-seven critically ill patients (21 males) were enrolled in the study; these included 13 nonobese, 12 obese, and 12 morbidly obese patients. All patients received dosing every 6 h, except for two patients (body mass indexes [BMIs], 40.9 and 53.3 kg/m^2) that received dosing every 12 h. In total, 222 blood samples were obtained from the participants. The demographic and clinical characteristics of the patients with the respective categorizations according to their BMIs are shown in Table 1. Only the total body weight (TBW), lean body weight (LBW), ideal body weight (IBW), and BMI were significantly different among the patients in the three BMI categorizations ($P < 0.05$).

TABLE 2 Parameter estimates for piperacillin from the final two-compartment covariate population PK model

Parameter[a]	Mean (SD)	Coefficient of variation (%)	Median
CL (liters/h)	14.0 (7.1)	51.38	10.72
V_1 (liters)	49.0 (19.0)	37.68	57.97
kcp (h^{-1})	0.9 (0. 6)	68.02	0.80
kpc (h^{-1})	2.3 (2.8)	120.360	1.36
O	0.4 (0.2)	43.87	0.27

[a]CL, population clearance of piperacillin; V_1, population volume of distribution of central compartment; kcp, rate constant for the piperacillin distribution from the central to the peripheral compartment; kpc, rate constant for the piperacillin distribution from the peripheral to the central compartment; *O*, scaling factor for obesity.

Pharmacokinetic model building. Piperacillin PK were best described using a two-compartment linear model. The goodness of fit of the model was improved by inclusion of the following covariates: measured creatinine clearance (CL_{CR}; normalized to 100 ml/min) for piperacillin clearance and BMI (normalized to 35 kg/m^2) for the piperacillin population volume of distribution of the central compartment (V_1). When these covariates were added, each resulted in a significant decrease in the log likelihood. The final covariate model was statistically significantly better than the structural model ($P < 0.05$). A scaling factor for obesity (*O*) was also included for V_1 and resulted in a significant improvement to the model ($P < 0.001$). The final covariate model was as follows: TV CL $=$ CL $\cdot$ (CL_{CR}/100) and TV $V_1 = V_1 \cdot [(\text{BMI}/35)^{0.75}] \cdot O$, where TV CL is the typical value of piperacillin clearance, CL is the population parameter estimate of piperacillin clearance, CL_{CR} is the measured creatinine clearance, TV V_1 is the typical value of the piperacillin volume of distribution in the central compartment, V_1 is the population parameter estimate of the piperacillin volume of distribution of the central compartment, BMI is body mass index, and *O* is a scaling factor for obesity.

The mean $\pm$ standard deviation (SD) population PK parameter estimates for the final covariate model are shown in Table 2. The diagnostic plots confirmed the appropriateness of the model, as shown in Fig. 1a to c. The effect of BMI on piperacillin clearance and the volume of distribution of the central compartment is shown in Fig. 2 and 3, respectively. The final covariate model was then used for Monte Carlo dosing simulations.

Dosing simulations. Monte Carlo simulations and the probability of target attainment (PTA) of an fT_{MIC} for 50% of the dosing interval for a 4-g piperacillin dose at various BMIs, for various measured CL_{CR}s, and for different dosing regimens are presented in Table 3. The results showed that a higher measured CL_{CR} was associated with a lower PTA in patients in the different BMI classes. At lower and moderate measured CL_{CR}s (30 and 50 ml/min, respectively), the intermittent dosing regimens of piperacillin at 4 g every 4 and 6 h showed similar PTAs for nonobese, obese, and morbidly obese patients. In contrast, piperacillin doses of 4 g every 8 h had variable PTAs at low to moderate measured CL_{CR}s between the patients in the different BMI classes. Moreover, the intermittent dosing regimens of piperacillin at 4 g every 4 h for patients with BMIs of 30 and 40 kg/m^2 showed PTAs (MICs $\leq$ 8 mg/liter) higher than those achieved for patients with a BMI of 20 kg/m^2 (MICs $\leq$ 4 mg/liter). All extended and continuous-infusion dosing regimens of piperacillin achieved the PK/PD targets up to an MIC of at least 8 mg/liter.

FTA. The fractional target attainment (FTA) for different simulated piperacillin dosing regimens and patient BMIs and measured CL_{CR}s for both directed and empirical coverage of infections caused by *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* are shown in Table 4. For *A. baumannii* empirical therapy, all piperacillin dosing regimens failed to achieve the 90% target in all patient groups, including in scenarios with a CL_{CR} of 30 ml/min. Only intermittent piperacillin dosing every 6 and 8 h failed to achieve the 90% target for *A. baumannii*-directed therapy in patients with BMIs of 20 and 30 kg/m^2 at a higher CL_{CR} (150

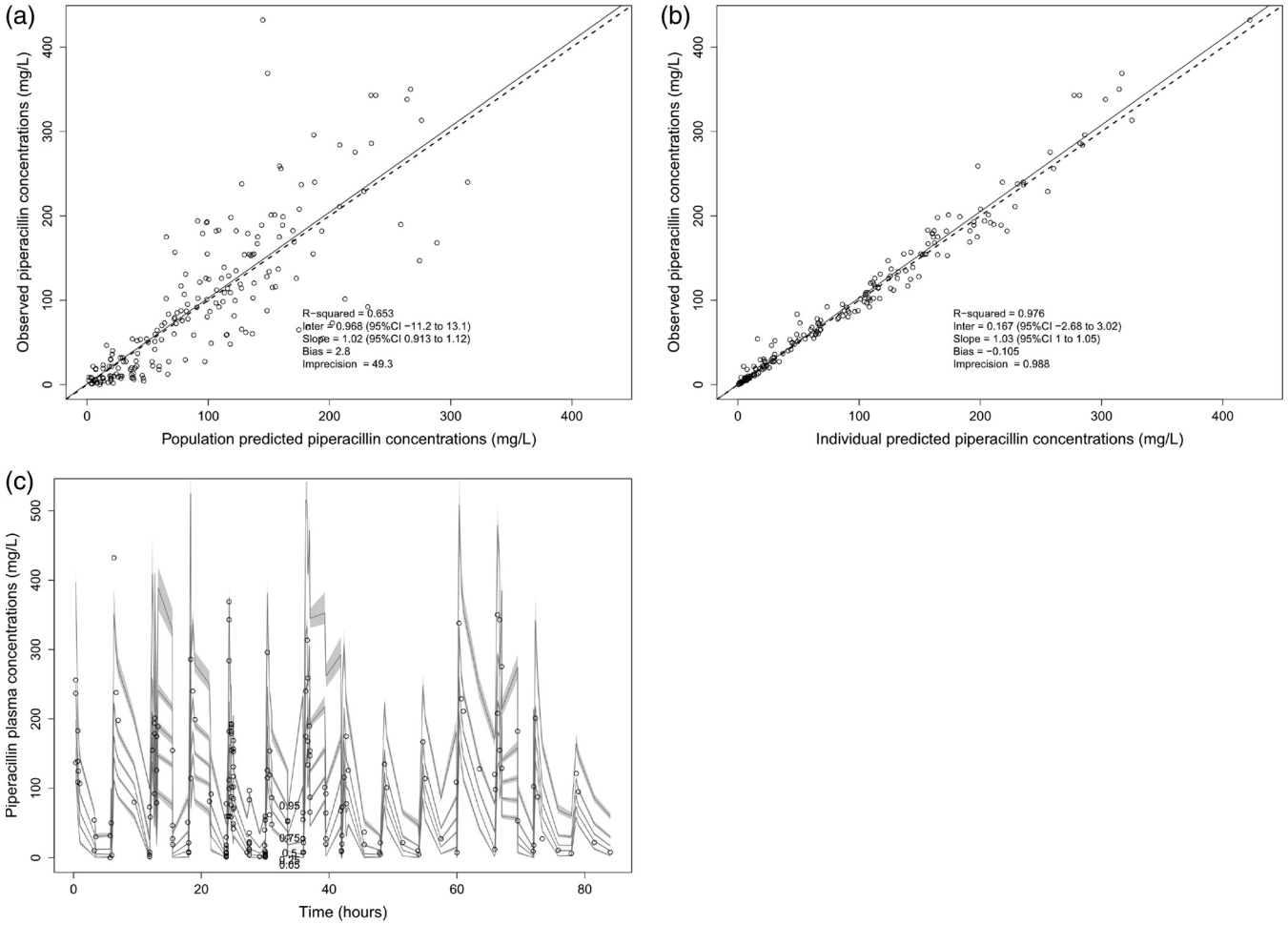

FIG 1 Diagnostic plots for the final population pharmacokinetic covariate model. (a) Observed piperacillin concentrations versus population predicted concentration (R^2 = 0.653); (b) observed piperacillin concentrations versus individual predicted concentrations (R^2 = 0.976); (c) visual predictive check. The median and 5th and 95th percentiles of simulated data with their respective 95% confidence intervals (CI; light gray fields) are shown. Individual points represent observed data. Inter, intercept.

ml/min). Prolonged piperacillin infusions as directed therapy achieved the 90% target for *E. coli*, *K. pneumoniae*, and *P. aeruginosa* in all groups of patients. Moreover, almost all piperacillin dosing regimens failed to achieve the 90% target for *P. aeruginosa* in all groups of patients, particularly in patients with CL_{CR}s of ≥50 ml/min.

DISCUSSION

Key findings. This is the first study of the population PK of piperacillin targeted at critically ill nonobese, obese, and morbidly obese patients. We found that both BMI and

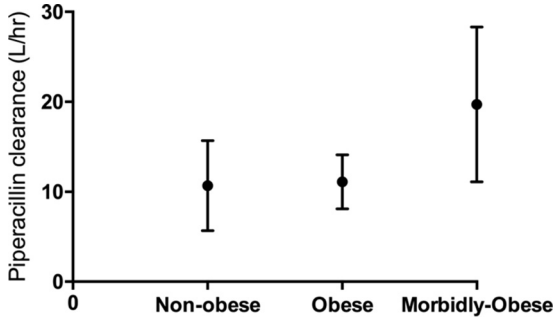

FIG 2 Effect of BMI class on piperacillin clearance.

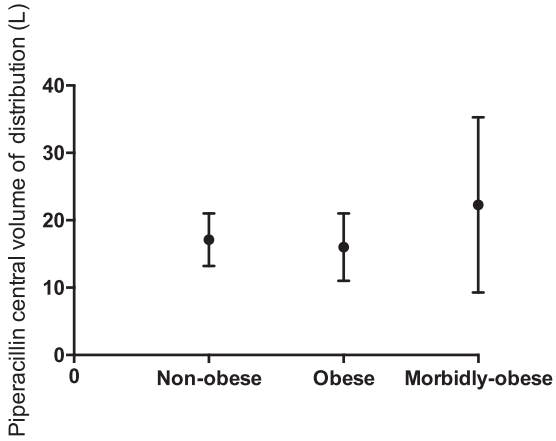

FIG 3 Effect of BMI class on the piperacillin volume of distribution of the central compartment.

CL_{CR} significantly affected piperacillin PK. Furthermore, as expected, we found that more frequent intermittent piperacillin doses produced a higher PTA across all BMI categories. We also found that piperacillin extended and continuous infusions greatly improved the PTA (an MIC up to at least 8 mg/liter) in the presence of different BMIs and measured CL_{CR}s. These data support those of other investigators (19–21), which suggest that extended and continuous infusions can normalize any effects of altered weight and renal function on achievement of therapeutic concentrations.

Relationship with previous papers. The PK of piperacillin in critically ill nonobese patients appear to be different from those in healthy subjects (22). This is likely due to the pathophysiological alterations that occur in critically ill patients, such as organ dysfunction, including renal and hepatic dysfunction, as well as fluid shifts and capillary permeability changes that can alter the piperacillin clearance and volume of distribution (12, 23). The presence of obesity may exaggerate these effects. However, to date, there is a shortage of studies on the PK of piperacillin in obese critically ill patients. Hites et al. (24) found that neither the piperacillin volume of distribution nor the piperacillin clearance was significantly different between obese and nonobese critically ill patients. However, the authors suggested that therapeutic drug monitoring (TDM) still be used for critically ill patients, including obese patients, as critically illness itself is responsible for largely unpredictable PK alterations.

In contrast, Sturm et al. (25) examined piperacillin PK in 9 morbidly obese critically ill patients and found that the volume of distribution of piperacillin in morbidly obese critically ill patients was higher than that in nonobese patients (31.0 liters versus 22.4 liters, respectively) and that the clearance of piperacillin was lower in morbidly obese critically ill patients than nonobese patients (6.0 liters/h versus 13.7 liters/h, respectively). At a piperacillin dose of 4 g administered over 30 min every 6 h, all patients in the study achieved the PK/PD target of an fT_{MIC} for 50% of the dosing interval when a higher MIC target (16 mg/liter) was used. The authors suggested that piperacillin administered as a 4-h extended infusion appears to have little advantage over piperacillin administered as a shorter 30-min infusion. This conclusion conflicts with our findings that showed that piperacillin extended and continuous infusions increased the rate of PK/PD target achievement compared to that achieved with intermittent regimens, particularly in patients with higher CL_{CR}s.

A large retrospective study of 1,400 patients by Alobaid et al. (26) examined the impact of obesity on the unbound plasma concentrations of piperacillin and meropenem. That study showed that obesity was associated with significantly lower unbound piperacillin concentrations in obese patients (29.4 mg/liter) than nonobese patients (42.0 mg/liter). Similarly, in the present study, we found that piperacillin clearance was higher in the morbidly obese group (19.7 $\pm$ 8.6 liters/h) than both the obese group (11.1 $\pm$ 3.0 liters/h) and the nonobese group (10.7 $\pm$ 5.0 liters/h), as shown

TABLE 3 PTA of piperacillin at 4 g for various BMIs, measured CL_{CR}s, dosing intervals, and durations of infusion[a]

Frequency and type of dosing	BMI (kg/m^2)	CL_{CR} (ml/min)	Achievement of PTA for MIC of: 0.25 mg/liter	0.50 mg/liter	1 mg/liter	2 mg/liter	4 mg/liter	8 mg/liter	16 mg/liter	32 mg/liter	64 mg/liter
Dosing every 4 h											
Intermittent	20	30	+	+	+	+	+	+	+	+	+
	20	50	+	+	+	+	+	+	+	+	−
	20	150	+	+	+	+	+	−	−	−	−
	30	30	+	+	+	+	+	+	+	+	+
	30	50	+	+	+	+	+	+	+	+	−
	30	150	+	+	+	+	+	+	−	−	−
	40	30	+	+	+	+	+	+	+	+	+
	40	50	+	+	+	+	+	+	+	+	−
	40	150	+	+	+	+	+	+	−	−	−
Extended infusion	20	30	+	+	+	+	+	+	+	+	+
	20	50	+	+	+	+	+	+	+	+	−
	20	150	+	+	+	+	+	+	+	−	−
	30	30	+	+	+	+	+	+	+	+	+
	30	50	+	+	+	+	+	+	+	+	−
	30	150	+	+	+	+	+	+	+	−	−
	40	30	+	+	+	+	+	+	+	+	+
	40	50	+	+	+	+	+	+	+	+	−
	40	150	+	+	+	+	+	+	+	−	−
Continuous infusion	20	30	+	+	+	+	+	+	+	+	+
	20	50	+	+	+	+	+	+	+	+	−
	20	150	+	+	+	+	+	+	+	−	−
	30	30	+	+	+	+	+	+	+	+	+
	30	50	+	+	+	+	+	+	+	+	−
	30	150	+	+	+	+	+	+	+	−	−
	40	30	+	+	+	+	+	+	+	+	+
	40	50	+	+	+	+	+	+	+	+	−
	40	150	+	+	+	+	+	+	+	−	−
Dosing every 6 h											
Intermittent	20	30	+	+	+	+	+	+	+	+	−
	20	50	+	+	+	+	+	+	+	−	−
	20	150	+	+	+	−	−	−	−	−	−
	30	30	+	+	+	+	+	+	+	+	−
	30	50	+	+	+	+	+	+	+	−	−
	30	150	+	+	+	+	−	−	−	−	−
	40	30	+	+	+	+	+	+	+	+	−
	40	50	+	+	+	+	+	+	+	−	−
	40	150	+	+	+	+	+	−	−	−	−
Extended infusion	20	30	+	+	+	+	+	+	+	+	−
	20	50	+	+	+	+	+	+	+	+	−
	20	150	+	+	+	+	+	+	−	−	−
	30	30	+	+	+	+	+	+	+	+	−
	30	50	+	+	+	+	+	+	+	+	−
	30	150	+	+	+	+	+	+	−	−	−
	40	30	+	+	+	+	+	+	+	+	−
	40	50	+	+	+	+	+	+	+	+	−
	40	150	+	+	+	+	+	+	−	−	−
Continuous infusion	20	30	+	+	+	+	+	+	+	+	+
	20	50	+	+	+	+	+	+	+	+	−
	20	150	+	+	+	+	+	+	−	−	−
	30	30	+	+	+	+	+	+	+	+	+
	30	50	+	+	+	+	+	+	+	+	−
	30	150	+	+	+	+	+	+	−	−	−
	40	30	+	+	+	+	+	+	+	+	+
	40	50	+	+	+	+	+	+	+	+	−
	40	150	+	+	+	+	+	+	−	−	−
Dosing every 8 h											
Intermittent	20	30	+	+	+	+	+	+	+	−	−
	20	50	+	+	+	+	+	+	−	−	−
	20	150	−	−	−	−	−	−	−	−	−
	30	30	+	+	+	+	+	+	+	+	−

(Continued on following page)

TABLE 3 (Continued)

Frequency and type of dosing	BMI (kg/m²)	CL_{CR} (ml/min)	Achievement of PTA for MIC of:								
			0.25 mg/liter	0.50 mg/liter	1 mg/liter	2 mg/liter	4 mg/liter	8 mg/liter	16 mg/liter	32 mg/liter	64 mg/liter
	30	50	+	+	+	+	+	+	−	−	−
	30	150	+	−	−	−	−	−	−	−	−
	40	30	+	+	+	+	+	+	+	+	−
	40	50	+	+	+	+	+	+	+	−	−
	40	150	+	+	−	−	−	−	−	−	−
Extended infusion	20	30	+	+	+	+	+	+	+	+	−
	20	50	+	+	+	+	+	+	+	−	−
	20	150	+	+	+	+	+	+	−	−	−
	30	30	+	+	+	+	+	+	+	+	−
	30	50	+	+	+	+	+	+	+	−	−
	30	150	+	+	+	+	+	+	−	−	−
	40	30	+	+	+	+	+	+	+	+	−
	40	50	+	+	+	+	+	+	+	−	−
	40	150	+	+	+	+	+	+	−	−	−
Continuous infusion	20	30	+	+	+	+	+	+	+	+	−
	20	50	+	+	+	+	+	+	+	−	−
	20	150	+	+	+	+	+	+	−	−	−
	30	30	+	+	+	+	+	+	+	+	−
	30	50	+	+	+	+	+	+	+	−	−
	30	150	+	+	+	+	+	+	−	−	−
	40	30	+	+	+	+	+	+	+	+	−
	40	50	+	+	+	+	+	+	+	−	−
	40	150	+	+	+	+	+	+	−	−	−

[a]The probability of target attainment was the probability that the free drug concentrations remains above the MIC for 50% of the dosing interval to achieve bactericidal activity. +, the probability of target attainment for piperacillin of at least 90% was achieved; −, the probability of target attainment for piperacillin failed to achieve a value of 90%; BMI, body mass index; CL_{CR}, measured creatinine clearance.

in Fig. 2. We also found that an increase in the BMI was significantly associated with an increase in V_1, highlighting the effect of an increase in obesity on likely changes in piperacillin exposure. This result is likely due to the consequent prolongation of the drug half-life associated with an increase in V_1, leading to more sustained periods when the concentrations exceed the therapeutic concentration target.

A study by Roberts et al. (22) investigated the PK of piperacillin administered by either continuous or intermittent dosing in critically ill patients with sepsis, including obese patients. The authors found that both the piperacillin volume of distribution and the piperacillin clearance were higher in critically ill patients with sepsis than healthy adults (25.0 liters versus 10.4 liters for the volume of distribution and 17.2 liters/h versus 11.3 liters/h for clearance) (27). The authors used a simulation approach to show that an increased length of infusion could increase the rate of achievement of therapeutic concentrations in the presence of the pathophysiological changes associated with critical illness. Furthermore, Cheatham et al. (28) found that the piperacillin volume of distribution and clearance were numerically higher in obese non-critically ill patients than in nonobese non-critically ill patients (33.4 liters versus 21.8 liters for volume of distribution and 13.7 liters/h versus 8.6 liters/h for clearance). The authors suggested that a higher piperacillin dose was necessary to ensure achievement of therapeutic concentrations.

Implications of study findings. Our results suggest that different piperacillin dosing regimens should be used to increase the rate of PK/PD target attainment in critically ill patients on the basis of their renal function and BMI. A 4-g piperacillin intermittent dose (administered every 6 and 8 h) for obese/nonobese critically ill patients with low to moderate measured CL_{CR}s appears to be appropriate for targeting pathogens with MICs of ≤8 mg/liter, such as *E. coli*. However, in patients with higher measured CL_{CR}s or when pathogens with higher MICs (≥16 mg/liter), such as *P. aeruginosa*, are suspected, the piperacillin dose is best given more frequently (every 4 h) to achieve PK/PD targets.

TABLE 4 FTA with piperacillin at 4 g for various BMIs, measured CL_{CR}s, dosing intervals, and methods of administrations for *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*[a]

			% patients infected with the following pathogen achieving the indicated MIC:							
			A. baumannii		*E. coli*		*K. pneumoniae*		*P. aeruginosa*	
Frequency and type of dosing	BMI (kg/m^2)	CL_{CR} (ml/min)	MIC for directed therapy	MIC for empirical therapy	MIC for directed therapy	MIC for empirical therapy	MIC for directed therapy	MIC for empirical therapy	MIC for directed therapy	MIC for empirical therapy
Dosing every 4 h										
Intermittent h	20	30	100.00	68.76	100.00	98.94	100.00	95.26	99.99	93.08
	20	50	99.96	55.60	99.98	98.02	99.96	92.04	99.92	87.18
	20	150	94.14	32.97	97.33	92.25	95.41	81.75	84.95	66.11
	30	30	100.00	67.86	100.00	98.91	100.00	95.09	100.00	92.82
	30	50	99.98	55.97	100.00	98.08	99.99	92.12	99.96	87.40
	30	150	97.41	35.45	98.92	94.16	98.06	84.75	91.33	71.35
	40	30	100.00	70.50	100.00	98.84	100.00	94.81	100.00	92.35
	40	50	100.00	55.84	100.00	98.08	100.00	92.07	99.99	87.35
	40	150	100.00	41.48	99.58	95.05	99.11	86.16	94.22	73.75
Extended infusion h	20	30	100.00	69.89	100.00	99.02	100.00	95.56	100.00	93.63
	20	50	100.00	57.80	100.00	98.24	100.00	92.55	100.00	88.32
	20	150	100.00	41.46	100.00	96.47	100.00	88.78	99.94	79.73
	30	30	100.00	67.72	100.00	98.90	100.00	95.05	100.00	92.76
	30	50	100.00	57.02	100.00	98.18	100.00	92.36	100.00	87.94
	30	150	100.00	40.25	100.00	96.27	100.00	88.45	99.78	78.90
	40	30	100.00	67.06	100.00	98.87	100.00	94.93	100.00	92.57
	40	50	100.00	56.53	100.00	98.14	100.00	92.24	100.00	87.70
	40	150	100.00	40.82	100.00	96.37	100.00	88.62	99.88	79.31
Continuous infusion	20	30	100.00	73.07	100.00	99.17	100.00	96.22	100.00	94.70
	20	50	100.00	59.57	100.00	98.36	100.00	92.96	100.00	89.09
	20	150	100.00	41.53	100.00	96.47	100.00	88.77	99.84	79.70
	30	30	100.00	71.72	100.00	99.12	100.00	96.00	100.00	94.34
	30	50	100.00	59.14	100.00	98.33	100.00	92.84	100.00	88.89
	30	150	100.00	41.51	100.00	96.46	100.00	88.76	99.84	79.68
	40	30	100.00	70.50	100.00	99.06	100.00	95.74	100.00	93.90
	40	50	100.00	58.63	100.00	98.30	100.00	92.70	100.00	88.65
	40	150	100.00	41.48	100.00	96.46	100.00	88.76	99.84	79.67
Dosing every 6 h										
Intermittent	20	30	99.98	57.38	100.00	98.18	99.99	92.48	99.95	88.07
	20	50	99.78	46.83	99.81	96.92	99.73	89.70	99.15	82.22
	20	150	79.81	25.04	84.98	79.73	78.24	65.64	58.69	45.08
	30	30	100.00	57.01	100.00	98.17	100.00	92.37	100.00	87.92
	30	50	99.93	47.85	99.97	97.25	99.93	90.15	99.69	83.13
	30	150	86.99	28.15	92.93	87.45	88.61	74.81	72.14	55.51
	40	30	100.00	56.33	100.00	98.11	100.00	92.18	100.00	87.58
	40	50	99.95	47.93	99.99	97.31	99.98	90.23	99.86	83.31
	40	150	91.32	29.91	96.11	90.57	93.15	78.85	78.96	60.80
Extended infusion	20	30	100.00	58.67	100.00	98.30	100.00	92.75	100.00	88.71
	20	50	100.00	58.67	100.00	98.23	100.00	92.75	100.00	88.71
	20	150	99.98	36.64	100.00	98.14	99.99	87.06	97.37	75.50
	30	30	100.00	57.72	100.00	98.30	100.00	92.52	100.00	88.25
	30	50	100.00	49.56	100.00	97.53	100.00	90.65	100.00	84.29
	30	150	99.98	36.33	100.00	97.47	99.99	86.91	97.01	75.13
	40	30	100.00	56.51	100.00	95.50	100.00	92.20	100.00	87.66
	40	50	100.00	49.00	100.00	95.42	100.00	90.52	100.00	84.01
	40	150	99.98	36.17	100.00	95.37	99.99	86.81	96.72	74.89
Continuous infusion	20	30	100.00	61.85	100.00	98.53	100.00	93.58	100.00	90.21
	20	50	100.00	51.71	100.00	97.72	100.00	91.15	100.00	85.36
	20	150	100.00	36.24	100.00	95.38	100.00	86.83	96.70	74.93
	30	30	100.00	60.93	100.00	98.47	100.00	93.34	100.00	89.79
	30	50	100.00	51.47	100.00	97.70	100.00	91.08	100.00	85.24
	30	150	100.00	36.24	100.00	95.38	100.00	86.83	96.72	74.93
	40	30	100.00	59.92	100.00	98.40	100.00	93.07	100.00	89.30
	40	50	100.00	51.14	100.00	97.68	100.00	90.99	100.00	85.07
	40	150	100.00	36.24	100.00	95.38	100.00	86.83	96.70	74.93

(Continued on following page)

TABLE 4 (Continued)

Frequency and type of dosing	BMI (kg/m²)	CL_{CR} (ml/min)	% patients infected with the following pathogen achieving the indicated MIC:							
			A. baumannii		*E. coli*		*K. pneumoniae*		*P. aeruginosa*	
			MIC for directed therapy	MIC for empirical therapy	MIC for directed therapy	MIC for empirical therapy	MIC for directed therapy	MIC for empirical therapy	MIC for directed therapy	MIC for empirical therapy
Dosing every 8 h										
Intermittent	20	30	99.89	49.53	99.97	97.40	99.93	90.54	99.62	83.93
	20	50	97.68	38.64	98.67	94.59	97.98	85.88	93.74	74.45
	20	150	56.54	16.86	49.48	46.23	40.36	33.54	24.71	18.86
	30	30	100.00	50.09	100.00	97.52	100.00	90.74	99.93	84.43
	30	50	99.15	40.78	99.63	95.88	99.35	87.74	97.16	77.74
	30	150	66.85	20.14	67.31	62.94	57.52	47.91	37.78	28.85
	40	30	100.00	50.01	100.00	97.54	100.00	90.72	99.97	84.44
	40	50	99.65	41.82	99.91	96.34	99.78	88.45	98.39	79.05
	40	150	73.43	22.36	78.50	73.47	69.42	57.94	47.90	36.60
Extended infusion	20	30	100.00	53.51	100.00	97.89	100.00	91.52	100.00	86.23
	20	50	100.00	45.99	100.00	97.12	100.00	89.85	100.00	82.39
	20	150	99.18	32.95	200.64	94.36	99.69	84.85	91.34	70.16
	30	30	100.00	52.23	100.00	97.77	100.00	91.21	100.00	85.59
	30	50	100.00	45.55	100.00	97.06	100.00	89.75	100.00	82.15
	30	150	99.25	33.08	99.88	94.41	99.72	84.94	91.62	70.38
	40	30	100.00	51.31	100.00	97.69	100.00	91.01	100.00	85.14
	40	50	100.00	45.07	100.00	97.00	100.00	89.64	99.99	81.88
	40	150	99.33	33.10	99.89	94.42	99.74	84.97	91.72	70.45
Continuous infusion	20	30	100.00	55.84	100.00	98.07	100.00	92.11	100.00	87.38
	20	50	100.00	47.21	100.00	97.25	100.00	90.14	100.00	83.04
	20	150	99.73	33.32	99.96	94.52	99.90	85.18	92.34	70.92
	30	30	100.00	55.39	100.00	98.04	100.00	91.99	100.00	87.15
	30	50	100.00	47.15	100.00	97.25	100.00	90.12	100.00	83.01
	30	150	99.73	33.32	99.96	94.52	99.90	85.18	92.34	70.92
	40	30	100.00	54.73	100.00	97.99	100.00	91.81	100.00	86.82
	40	50	100.00	47.05	100.00	97.24	100.00	90.09	100.00	82.96
	40	150	99.73	33.31	99.96	94.52	99.90	85.17	92.32	70.91

[a]Shading indicates piperacillin FTA attainment failed to achieve 90%. BMI, body mass index; CL_{CR}, creatinine clearance.

Furthermore, less frequent prolonged piperacillin infusions could also be considered when targeting pathogens with MICs of ~8 mg/liter in obese/nonobese critically ill patients, including those patients with a higher measured CL_{CR}. Prolonged piperacillin infusion (e.g., 4 g every 6 h as a 3-h infusion) is recommended for the targeting of pathogens with MICs of ~16 mg/liter for patients with a higher measured CL_{CR} (150 ml/min). However, knowledge of patient renal function is important and should be used for more accurate dose individualization.

When piperacillin is considered for empirical therapy, all dosing regimens failed to achieve the 90% target for both *A. baumannii* and *P. aeruginosa*. In such cases it would appear that combination therapy would be appropriate to ensure maximal therapy.

Study limitations. Although this study is the first study of the population PK of piperacillin in critically ill nonobese, obese, and morbidly obese patients, it has some limitations that should be declared. First, even though the drug formulation contained both piperacillin (a β-lactam antibiotic) and tazobactam (a β-lactamase inhibitor), we did not measure tazobactam concentrations. Second, even though this is considered a relatively large PK study in critically ill patients, the sample size would not be considered sufficient for quantifying the effect of piperacillin exposure on patient outcome. Finally, we collected only blood samples, which may not necessarily indicate the concentrations at the site of infection, and more specific mechanistic studies would be required to determine penetration into the interstitial fluid of different tissues of obese and morbidly obese patients.

Conclusion. In summary, this study presents the first population PK study of piperacillin in critically ill patients in three different BMI categories. Although an increase in the BMI does not appear to have a large effect on the probability of PK/PD

target attainment in critically ill patients, an increase in the measured CL_{CR} was strongly associated with a lower probability of PK/PD target attainment. A piperacillin dose of 4 g every 4, 6, or 8 h as a prolonged infusion is required to achieve the PK/PD targets. Also, the use of more frequent intermittent or higher intermittent doses provides another option for less susceptible pathogens, including *P. aeruginosa*, and/or in critically ill obese and nonobese patients with high CL_{CR}s. TDM of piperacillin should be used where available for dose optimization.

MATERIALS AND METHODS

Setting. This was an observational PK study at a tertiary referral intensive care unit (ICU). Ethical approval was obtained from the Queensland Royal Brisbane and Women's Hospital Human Research Ethics Committee (HREC/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 (i) an age of ≥18 years, (ii) treatment with piperacillin, and (iii) a BMI of ≥18.5 kg/m^2. The exclusion criteria were (i) renal replacement therapy (RRT), (ii) pregnancy for women, (iii) active bleeding, and (iv) HIV infection or hepatitis.

Study protocol. Piperacillin was administered at the discretion of the treating clinician at dosage regimens of 4 g every 6 or 12 h as a 20-min infusion. Participants were categorized into one of three groups according to their BMI, as follows: normal weight (BMI = 18.5 to 29.9 kg/m^2), obese (BMI = 30 to 39.9 kg/m^2), and morbidly obese (BMI ≥ 40 kg/m^2). During one dosing interval, blood samples (≈3 ml) were taken from each participant to determine total plasma piperacillin concentrations at the following times: before administration of the dose and at 20 min (the end of infusion), 40 min, and 1, 3.5, and 6 h after administration of the dose. Clinical and demographic data were collected on the day of sampling, including age, sex, total body weight (TBW), ideal body weight (IBW), lean body weight (LBW), and BMI, (29). Clinical data were also recorded, including Sequential Organ Failure Assessment (SOFA) (30) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (31), as well as the serum albumin and serum creatinine concentrations and the CL_{CR} estimated by the Cockcroft-Gault equation (32) separately using TBW, LBW, and IBW. Urine samples were also collected over the dosing interval to determine the measured CL_{CR}.

Sample handling, storage, and assay. Blood samples were placed in an ice bath immediately upon collection and centrifuged at 3,000 rpm for 10 min. Plasma samples were stored at −80°C until bioanalysis. The piperacillin concentration (0.5 to 500 mg/liter) in plasma was measured by a validated ultra-high-performance liquid chromatography (UHPLC)-tandem mass spectrometry (MS/MS) method on a Shimadzu Nexera2 UHPLC system coupled to a Shimadzu 8030+ triple quadruple mass spectrometer (Shimadzu, Kyoto, Japan). Clinical samples were assayed alongside plasma calibrators and quality controls and met batch acceptance criteria (33).

Plasma (2.5 μl) was spiked with the internal standard ([*d5*]-piperacillin), treated with acetonitrile, and centrifuged. The supernatant (0.5 μl) was injected into the UHPLC-MS/MS. The stationary phase was a C_{18} Shimadzu Shim-pack XR-ODS III 1.6-μm column (Shimadzu, Kyoto, Japan) operated at room temperature. Mobile phase A was 0.1% (vol/vol) formic acid in water, and mobile phase B was 100% acetonitrile with 0.1% (vol/vol) formic acid. The gradient went from 7.5% mobile phase B to 95% mobile phase B and back again for an 8.0-min run time. The flow rate was 0.3 ml/min and produced a backpressure of about 5,000 lb/in^2. Piperacillin was monitored by positive mode electrospray at a multiple reaction monitoring level of 518.00 → 143.00. [*d5*]-piperacillin was monitored in the positive mode at 523.00 → 148.00.

The assay method was validated for linearity, matrix test, selectivity, lower limit of quantitation, recovery, reinjection stability, precision, and accuracy using the FDA criteria for bioanalysis (33). Precision was within 5.8% and accuracy was within 10.0% at the tested plasma quality control piperacillin concentrations of 1.5, 50, and 400 mg/liter.

Population pharmacokinetic modeling. One- and two-compartment models were developed using the nonparametric adaptive grid algorithm within the Pmetrics package for R (Los Angeles, CA, USA) (34, 35).

We tested demographic and clinical characteristics for inclusion as covariates if they were biologically plausible for affecting piperacillin PK. The covariates assessed included age, sex, TBW, IBW, LBW, BMI, serum creatinine concentration, measured CL_{CR}, CL_{CR} estimated by the Cockcroft-Gault equation (separately using TBW, LBW and IBW), albumin concentration, SOFA score, and APACHE II score. Covariates that significantly reduced the log likelihood ($P < 0.05$) and/or improved the goodness-of-fit plots were included in the model.

Model diagnostics. The goodness of fit of each model was evaluated by visual inspection of the observed-predicted (population and individual) concentration scatter plots. The coefficient of determination of the linear regression of the observed-predicted values and the log likelihood values from each run were also used to assess the goodness of fit. The predictive performance was evaluated using the mean prediction error (bias) and mean bias-adjusted squared prediction error (imprecision) for the population and individual predicted concentrations in the central compartment. The suitability of the final covariate model was assessed using a visual predictive check (VPC) after bootstrap resampling method (n = 1,000 simulations) and normalized prediction distribution errors (36).

PTA. Monte Carlo simulations (n = 1,000) were performed using Pmetrics software to determine the probability of target attainment (PTA) of an fT_{MIC} of 50% of the dosing interval (18) for a variety of MICs

and for measured CL_{CR} and BMI classes. Piperacillin doses of 4 g intravenously every 4, 6, and 8 h as a 30-min intermittent infusion, a 2-h (dosing every 4 h), 3-h (dosing every 6 h), or 4-h (dosing every 8 h) extended infusion, or a continuous infusion (after administration of a 4-g loading dose over 30 min) were simulated at three different levels of renal function (measured CL_{CR}s = 30, 50 and 150 ml/min) and three BMI classes of 20, 30, and 40 kg/m^2.

Calculation of FTA. MIC data for *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were used to determine the fractional target attainment (FTA) according to the MIC distributions from the European Committee for Antimicrobial Susceptibility and Testing (EUCAST) database (37). The FTA compares the PK/PD exposure (PTA) against an MIC distribution to identify the rate of achievement of the target piperacillin exposure against the distribution of susceptibilities of the pathogen. A piperacillin dosing regimen was considered successful if the FTA value was ≥90%. MIC distributions for susceptibility for these pathogens (an MIC of ≤8 mg/liter for *A. baumannii*, *E. coli*, and *K. pneumoniae* and an MIC of ≤16 mg/liter *P. aeruginosa*) were used to determine the FTA for directed therapy. Additionally, we used the entire MIC distribution (MICs for the susceptibility and resistance of the isolates) to determine the FTA, as would be encountered with empirical monotherapy.

Statistical analysis. Demographic data were analyzed using the statistical software package IBM-SPSS statistics (version 22.0; IBM, New York, NY, USA). Continuous variables were defined as the mean (standard deviation [SD]). A P value of <0.05 was considered statistically significant.

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