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What is the effect of obesity on piperacillin and meropenem trough concentrations in critically ill patients?

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Objectives: The objectives of this study were to determine the effects of obesity on unbound trough concentrations and on the achievement of pharmacokinetic (PK)/pharmacodynamic (PD) targets of piperacillin and meropenem in critically ill patients.

Methods: This study retrospectively analysed therapeutic-drug-monitoring data from ICU databases in Australia, Germany and Spain, as well as from a large PK study. The presence of obesity was defined as a BMI ≥30 kg/m^2, and patients were also categorized based on level of renal function. The presence of obesity was compared with unbound piperacillin and meropenem trough concentrations. We also used logistic regression to describe factors associated with the achievement of the PK/PD targets, an unbound concentration maintained above the MIC breakpoint (100% $fT_{>MIC}$ and 100% $fT_{>4\times MIC}$) of *Pseudomonas aeruginosa*.

Results: In all, 1400 patients were eligible for inclusion in the study. The median age and weight were 67 years (IQR 52–76 years) and 79 kg (69–90 kg), respectively, and 65% of participants were male. Significantly lower median piperacillin trough concentrations [29.4 mg/L (IQR 17.0–58.0 mg/L)] were found in obese patients compared with non-obese patients [42.0 mg/L (21.5–73.5 mg/L)] ($P=0.001$). There was no difference for meropenem trough concentrations [obese 10.3 mg/L (IQR 4.8–16.0 mg/L) versus non-obese 11.0 mg/L (4.3–18.5 mg/L); $P=0.296$]. Using logistic regression, we found that the presence of obesity was not associated with achievement of 100% $fT_{>MIC}$, but the use of prolonged infusion, a creatinine clearance ≤100 mL/min, increasing age and female gender were for various PK/PD targets for both piperacillin and meropenem ($P<0.05$).

Conclusions: This large dataset has shown that the presence of obesity in critically ill patients may affect piperacillin, but not meropenem, unbound trough concentrations.

Introduction

β-Lactam antibiotics, such as meropenem and piperacillin, are frequently prescribed in critically ill patients.[1–3] Recent studies have shown that there is considerable variation in the β-lactam pharmacokinetics (PK) in some populations.[4–6] Obesity has previously been proposed to be a risk factor for altered β-lactam concentrations in critically ill and non-critically ill patients.[7–9] Consequently, with the increased prevalence of obesity in Western society, ensuring β-lactam antibiotics reach therapeutic concentrations in obese critically ill patients is considered to be a serious challenge for clinicians.[10–13] Dose-finding studies include neither obese nor critically ill patients, and current data for obese critically ill patients show significantly wider variability in the PK of β-lactam antibiotics compared with those of non-obese critically ill patients.[7,14] This PK variability results from the physiological changes caused by obesity, which may alter both the volume of distribution and clearance of the drug.[15] In the presence of critical illness, these PK effects may escalate into augmented renal clearance (ARC) or acute kidney injury.[16–18] These changes in drug disposition heighten the challenge of dosing in obese critically ill patients.[16–18]

We are not aware of any available dosing guidelines for critically ill obese patients.[14,19] Although Hites and Taccone[20] have provided a very useful recent review on the optimization of β-lactam

dosing in critically ill obese patients, the certainty of the recommendations are unclear. In their review, only single-centre small PK studies and case series were available, and very few of them compared results from obese patients with those of non-obese critically ill patients.

Therefore, the aim of this study was to compare piperacillin and meropenem trough concentrations, as well as the achievement of PK/pharmacodynamic (PD) targets, in critically ill obese and non-obese patients.

Methods

Study design and setting

This study retrospectively analysed data from therapeutic drug monitoring (TDM) databases from three ICUs—the Royal Brisbane & Women's Hospital, Australia; Heidenheim Hospital, Germany; and Hospital del Mar, Spain—as well as from the Defining Antibiotic Levels in ICU (DALI) multicentre point-prevalence PK study in 68 ICUs.[21] In these datasets, blood samples had been collected from critically ill patients treated with meropenem and piperacillin. All plasma samples were assayed using validated chromatographic methods. In samples from Australia and the DALI study, unbound concentrations were directly measured, whilst in those from Germany and Spain, total antibiotic concentrations were measured. For the latter two groups, unbound concentrations were then calculated using protein-binding percentages for piperacillin (30%) and meropenem (2%), as recommended by Wong *et al.*[22]

Ethics approval for this study was granted by the Human Research Ethics Committee, Royal Brisbane and Women's Hospital, Brisbane, Australia (HREC/14/QRBW/534).

Meropenem and piperacillin/tazobactam were dosed according to the treating clinicians' decision. Dosing was administered by either intermittent or prolonged infusion. Prolonged infusion was defined as an infusion >2 h, including administration by continuous infusion.

Patients

Critically ill patients were included in the study if they met the following inclusion criteria: age ≥18 years; BMI ≥18.5 kg/m^2; treatment with meropenem or piperacillin; and a complete set of data for all variables. Exclusion criteria were as follows: age <18 years; BMI <18.5 kg/m^2; and missing data. Patients were categorized into two BMI categories of non-obese (BMI from 18.5 to 29.9 kg/m^2) and obese (BMI ≥30 kg/m^2). Furthermore, patients were categorized according to creatinine clearance (CL_{CR}), which was calculated using the Cockcroft–Gault equation, into classes 1 (≤25 mL/min), 2 (>25 to ≤50 mL/min), 3 (>50 to ≤100 mL/min) and 4 (>100 mL/min).

Approaches to dosing across the Australian and Spanish groups, as well as the DALI study, were similar, with all patients receiving standard dosing for both piperacillin (12–16 g per 24 h in 3–4 divided doses) and meropenem (2–3 g per 24 h in 2–3 divided doses). However, the patients from Germany received a nomogram-derived CL_{CR}-based continuous infusion of antibiotic, where CL_{CR} was calculated using the Cockcroft–Gault equation with ideal body weight.

Data collection

Demographic and clinical information, including age, sex, height, weight, BMI, serum creatinine concentration and unbound trough concentrations for meropenem or piperacillin, was extracted from the databases. The duration of antibiotic infusion was also collected. CL_{CR} was calculated using the actual body weight of the patients.[23] The total daily dose of the study antibiotics was calculated from the prescribed dose strength and frequency.

PK/PD target attainment

To investigate the effect of obesity on PK/PD target attainment, the following PK/PD targets were assessed:[21,24] (i) 100% of the dosing interval that the unbound concentration of antibiotic exceeds the MIC ($fT_{>MIC}$); (ii)

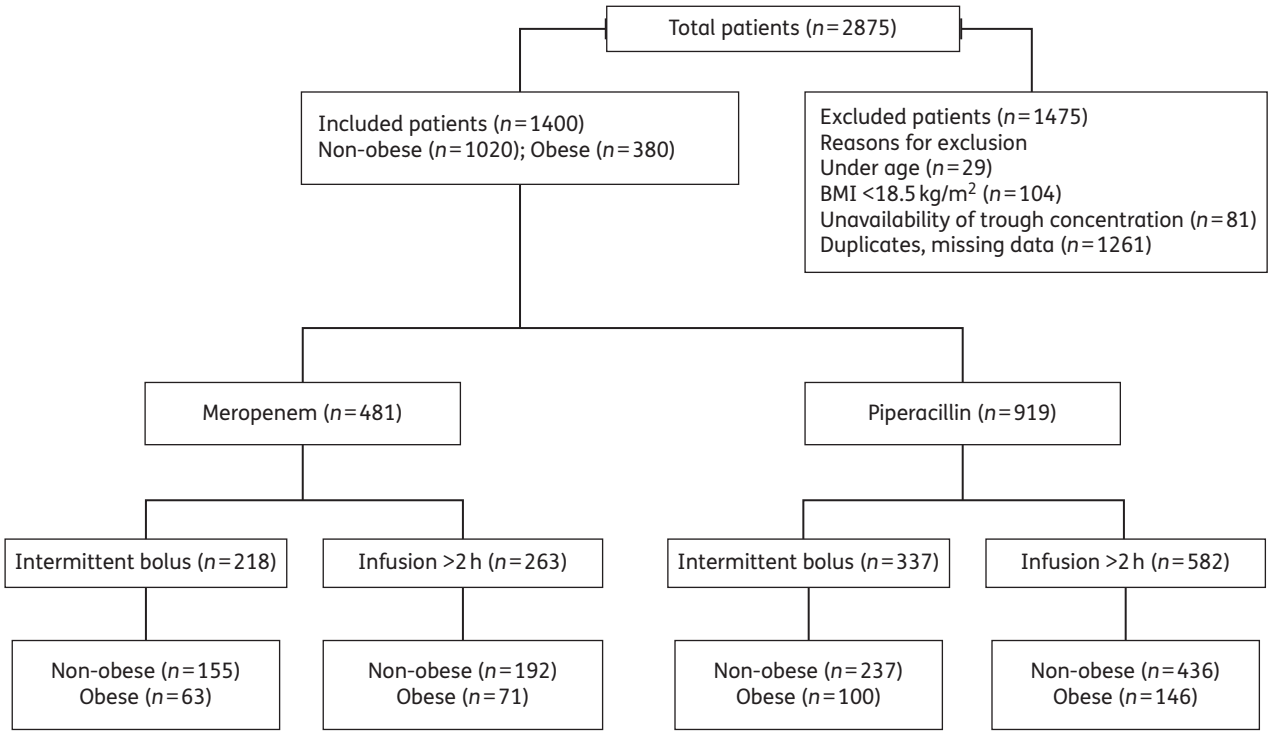

Figure 1. Study flow chart.

100% of the dosing interval that the unbound concentration of antibiotic exceeds 4×MIC ($fT_{>4\times MIC}$).

Although these targets are higher than the PK/PD exposures suggested by *in vitro* PD studies,[25] these are common TDM targets for sites using TDM for piperacillin and meropenem.[3,26] As both agents have anti-pseudomonal activity, we chose the MIC breakpoints for susceptibility from EUCAST for this analysis: meropenem, 2 mg/L; and piperacillin, 16 mg/L.

Statistical analysis

Continuous variables are expressed as median values and IQRs and categorical variables are expressed as absolute and relative frequencies. The Kolmogorov–Smirnov test was used to test for normality. Linear variables were compared using Mann–Whitney *U*-test. Dichotomous variables were compared using the Pearson χ^2 test or Fisher's exact test as appropriate. To describe the factors affecting attainment of PK/PD targets, factors with a *P* value ≤0.15 by univariate analysis were then included in the multivariate analysis. The ORs and bootstrapped 95% CIs were obtained using binary logistic regression. All statistical analyses were performed using the statistical software package IBM-SPSS statistics 22.0 (IBM, New York, USA). A two-sided *P* value <0.05 was considered statistically significant.

Results

Demographic and clinical data

From the 2875 patients across the combined datasets, 1400 critically ill patients met the inclusion criteria for this study (Figure 1). Significant differences were found between the obese and non-obese patients for age [65 years (IQR 51–74 years) versus 68 years (IQR 53–76 years); $P=0.040$], height [170 cm (IQR 160–177 cm) versus 170 cm (IQR 165–176 cm); $P=0.029$], weight [100 kg (IQR 90–115 kg) versus 73 kg (IQR 65–80 kg); $P<0.001$], BMI [34 kg/m^2 (IQR 31–39 kg/m^2) versus 25 kg/m^2 (IQR 23–27 kg/m^2); $P<0.001$], serum creatinine concentration

Table 1. Patient characteristics: demographic and clinical data according to PK/PD achievement

	Plasma antibiotic concentration over MIC achievement					
	$fT_{>MIC}$			$fT_{>4\times MIC}$		
	achieved	not achieved	*P*	achieved	not achieved	*P*
Age (years), median	65.4	46.8	<0.001	70.0	57.3	<0.001
Male, *n* (%)	732 (64.4)	180 (68.7)	<0.001	394 (58.4)	518 (71.5)	<0.001
Height (cm), median	169.9	169.6	<0.001	169.0	172.0	<0.001
Weight (kg), median	81.2	80.0	0.055	78.1	85.0	<0.001
BMI (kg/m^2), median	28.1	28.0	0.965	27.7	28.8	0.032
Meropenem, *n* (%)	404 (84.0)	77 (16.0)	0.034	297 (61.7)	184 (38.3)	<0.001
Piperacillin, *n* (%)	733 (79.8)	185 (20.2)		378 (41.2)	540 (58.8)	
Serum creatinine (μmol/L), median	140	58.2	<0.001	181.2	100.3	<0.001
CL_{CR} (mL/min)[a], median	72.6	161.5	<0.001	48.4	104.3	<0.001

The *P* value tested the significance of difference between the obese and non-obese patients.
[a]Estimated with the Cockcroft–Gault equation.

Table 2. Total daily doses and duration of infusion and unbound trough concentration data for piperacillin and meropenem for obese and non-obese groups

	Piperacillin				Meropenem			
	all patients (*n*=919)	obese (*n*=246)	non-obese (*n*=673)	*P*	all patients (*n*=481)	obese (*n*=134)	non-obese (*n*=347)	*P*
Total daily dose (g), median (IQR)	12.0 (8.0–16.0)	12.0 (12.0–16.0)	12.0 (8.0–16.0)	0.126	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	0.248
Method of infusion, *n* (%)				0.130				0.643
intermittent bolus	337 (36.7)	100 (40.7)	237 (35.2)		218 (45.3)	63 (47.0)	155 (44.7)	
prolonged infusion	582 (63.3)	146 (59.3)	436 (64.8)		263 (54.7)	71 (53.0)	192 (55.3)	
Trough concentration (mg/L), median (IQR)	38.5 (19.7–70.0)	29.4 (17.0–58.0)	42.0 (21.5–73.5)	0.001	11.0 (4.4–17.5)	10.3 (4.8–16.0)	11.0 (4.3–18.5)	0.296

The *P* value tested the significance of difference between the obese and non-obese patients.

[109 μmol/L (IQR 74–189 μmol/L) versus 92 μmol/L (IQR 64–157 μmol/L); $P<0.001$] and CL_{CR} [73 mL/min (IQR 42–124 mL/min) versus 59 mL/min (IQR 34–99 mL/min); $P<0.001$]. Table 1 displays the demographic and clinical factors for all patients that were associated with achievement of PK/PD targets.

Dosing and concentration data

Table 2 presents the total daily dose and unbound trough concentration data comparison between obese and non-obese patients. Of the patients categorized as receiving prolonged infusion, 226/263 (86.0%) meropenem patients and 538/582 (92.4%) piperacillin patients received continuous infusions. No significant differences between the BMI groups were found for the total daily dose or duration of infusion for either piperacillin or meropenem. Significantly lower trough concentrations were found for piperacillin in the critically ill obese patient group.

Differences in trough concentration between obese and non-obese patients

Table 3 shows the differences in trough concentrations between obese and non-obese critically ill patients relative to duration of infusion and the different CL_{CR} classes. No significant differences in trough concentration between the obese and non-obese groups were found.

PK/PD target achievement

Table 4 presents the piperacillin and meropenem data for the achievement of PK/PD targets. There was no significant difference between obese and non-obese patients for achievement of $fT_{>MIC}$ for either antibiotic. A significantly lower percentage of obese patients achieved $fT_{>4\times MIC}$ for piperacillin, although the frequency of target attainment was low for both obese and non-obese patients.

Factors predicting $fT_{>MIC}$ and $fT_{>4\times MIC}$

The factors that predicted the achievement of the PK/PD targets ($fT_{>MIC}$ and $fT_{>4\times MIC}$) are shown in Table 5. We found that prolonged infusion, a $CL_{CR} \leq 100$ mL/min, greater age and female gender were all associated with the achievement of $fT_{>MIC}$ for piperacillin. Higher total daily dose, $CL_{CR} \leq 100$ mL/min and female gender were associated with the achievement of $fT_{>4\times MIC}$ for piperacillin. Prolonged infusion, CL_{CR} >50 to ≤100 mL/min and greater age were associated with the achievement of $fT_{>MIC}$ for meropenem, whereas prolonged infusion, a $CL_{CR} \leq 100$ mL/min, greater age and female gender were all associated with the achievement of $fT_{>4\times MIC}$. The presence of obesity was not a significant factor associated with the achievement of the chosen PK/PD targets for either antibiotic.

Discussion

There is a dearth of large studies describing the effect of obesity on β-lactam concentrations and PK/PD target achievement in critically ill patients. In our study, we found that patients classified to be obese (BMI ≥30 kg/m^2) had lower unbound trough concentrations for piperacillin, but not for meropenem, than

Table 3. Effects of obesity on piperacillin and meropenem unbound trough concentrations according to duration of infusion and CL_{CR} for prolonged infusion versus intermittent bolus

	Piperacillin trough concentration (mg/L)				Meropenem trough concentration (mg/L)			
CL_{CR} (mL/min)	all patients ($n=576$)	obese ($n=144$)	non-obese ($n=432$)	*P*	all patients ($n=260$)	obese ($n=71$)	non-obese ($n=189$)	*P*
Prolonged infusion								
≤25	$n=118$ 106 (72–140)	$n=24$ 78 (54–154)	$n=94$ 107 (78–137)	0.494	$n=45$ 21 (15–27)	$n=9$ 16 (9–28)	$n=36$ 22 (16–27)	0.626
>25 to ≤50	$n=147$ 84 (58–116)	$n=28$ 76 (48–104)	$n=119$ 85 (60–116)	0.309	$n=75$ 18 (15–25)	$n=19$ 16 (15–20)	$n=56$ 19 (16–27)	0.365
>50 to ≤100	$n=211$ 57 (40–83)	$n=52$ 49 (32–79)	$n=159$ 59 (43–84)	0.608	$n=75$ 15 (10–18)	$n=21$ 15 (12–18)	$n=54$; 15 (10–18)	0.765
>100	$n=100$ 35 (26–51)	$n=40$ 34 (27–47)	$n=60$ 39 (25–55)	0.555	$n=65$ 8 (4–12)	$n=22$ 8 (5–12)	$n=43$ 8 (3–12)	0.491
Intermittent bolus								
≤25	$n=31$ 103 (48–141)	$n=6$ 79 (40–108)	$n=25$ 112 (57–162)	0.478	$n=17$ 12 (10–17)	$n=2$ 10 (10–10)	$n=15$ 13 (10–17)	0.592
>25 to ≤50	$n=63$ 47 (16–90)	$n=18$ 69 (15–100)	$n=45$ 44 (17–84)	0.568	$n=51$ 11 (6–15)	$n=16$ 13 (8–18)	$n=35$ 9 (5–14)	0.639
>50 to ≤100	$n=113$ 21 (10–51)	$n=35$ 19 (11–54)	$n=78$ 22 (8–51)	0.447	$n=58$ 7 (3–14)	$n=20$ 7 (3–18)	$n=38$ 7 (4–14)	0.552
>100	$n=125$ 6 (2–15)	$n=40$ 5 (2–18)	$n=85$ 7 (2–13)	0.668	$n=83$ 1 (0–5)	$n=22$ 1 (0–5)	$n=61$ 1 (0.4–5)	0.662

Data are presented as median (IQR).
The *P* value tested the significance of difference between the obese and non-obese patients.

those of non-obese patients. We observed that 23.7% and 14.2% of obese patients did not achieve 100% $fT_{>MIC}$ for piperacillin and meropenem, respectively, whereas this target was not achieved in 19.8% and 16.7%, respectively, of non-obese patients. For a higher PK/PD target of 100% $fT_{>4\times MIC}$, only piperacillin was associated with a significantly lower target attainment in the obese group, although target attainment was low for both obese and non-obese patients.

These results of our study do not align with the findings of the only other similar study of critically ill patients comparing obese and non-obese patients. In that study, by Hites *et al.*,[7] meropenem concentrations were found to be lower in obese than in non-obese critically ill patients, with no significant difference found for piperacillin between these two groups. The difference between the findings of the Hites *et al.*[7] study and those of our study could be due to the different case mix of the patients from the studies and the different empirical approaches to dosing across the respective patient cohorts. The present results are consistent with studies of obese cohorts that found both meropenem and piperacillin achieved 100% $fT_{>MIC}$ in many patients,[9,14,27,28] although we believe that 23.7% of patients not achieving the target for piperacillin, in particular, is a value that as clinicians we should aim to improve.

Of interest, the statistical significance of obesity for affecting PK/PD target attainment for piperacillin in the univariate analysis was not found to be significant in the logistic regression (Table 5). The factors associated with achieving the lower PK/PD target, 100% $fT_{>MIC}$, for both antibiotics included use of prolonged infusion, a lower CL_{CR} defined as ≤100 mL/min and increasing age. This result is unsurprising, as use of prolonged infusions has been shown in simulation studies to increase $fT_{>MIC}$, as has the presence of reduced renal function, which is also more common in older patients. The daily dose was interestingly not found to be associated with achievement of $fT_{>MIC}$, and this finding may be because there was not a wide range of doses used in the study, or, alternatively, because the minor dose adjustments that were made for different levels of renal function prevented this being significant. For the higher PK/PD target, 100% $fT_{>4\times MIC}$, only a lower CL_{CR} defined as

Table 4. Piperacillin and meropenem achievement of PK/PD targets

PK/PD index	All patients	Obese	Non-obese	*P*
Piperacillin				
$fT_{>MIC}$, *n* (%)	727 (79.1)	178 (76.3)	540 (80.2)	0.097
$fT_{>4\times MIC}$, *n* (%)	259 (28.2)	51 (20.7)	208 (30.9)	0.002
Meropenem				
$fT_{>MIC}$, *n* (%)	404 (84.0)	115 (85.8)	289 (83.3)	0.298
$fT_{>4\times MIC}$, *n* (%)	279 (61.7)	80 (59.7)	217 (62.5)	0.566

The *P* value tested the significance of difference between the obese and non-obese patients.

Table 5. Binary logistic regression of factors predicting $fT_{>MIC}$ and $fT_{>4\times MIC}$

	OR (95% CI)			
	piperacillin	*P*	meropenem	*P*
Factors predicting $fT_{>MIC}$				
prolonged infusion	8.39 (5.35–13.17)	<0.001	7.80 (3.72–16.38)	<0.001
daily dose	1.07 (0.98–1.16)	0.123	0.86 (0.72–1.03)	0.091
CL_{CR} ≤50 (mL/min)	3.53 (2.11–5.92)	<0.001	3.40 (0.86–13.51)	0.082
CL_{CR} >50 to ≤100 (mL/min)	14.08 (7.41–27.08)	<0.001	21.74 (6.02–76.92)	<0.001
CL_{CR} >100 (mL/min)	1.00		1.00	
age (years)	1.02 (1.00–1.03)	0.012	1.04 (1.01–1.06)	0.002
gender (male)	0.43 (0.28–0.64)	<0.001	1.14 (0.59–2.22)	0.700
BMI (kg/m^2)	0.77 (0.52–1.15)	0.203	1.29 (0.62–2.66)	0.496
Goodness-of-fit (Hosmer–Lemeshow test)	χ^2=11.109, *df*=8	0.196	χ^2=2.428, *df*=8	0.965
Factors predicting $fT_{>4\times MIC}$				
prolonged infusion	0.70 (0.42–1.18)	0.183	7.31 (4.32–12.37)	<0.001
daily dose	1.10 (1.02–1.20)	0.021	1.04 (0.88–1.23)	0.665
CL_{CR} ≤50 (mL/min)	5.81 (3.44–9.80)	<0.001	3.44 (1.86–6.37)	<0.001
CL_{CR} >50 to ≤100 (mL/min)	166.6 (2.17–1000.00)	<0.001	20.83 (9.52–45.45)	<0.001
CL_{CR} >100 (mL/min)	1.00		1.00	
age (years)	0.99 (0.98–1.01)	0.639	1.02 (1.00–1.04)	0.014
gender (male)	0.29 (0.19–0.46)	<0.001	0.36 (0.20–0.62)	<0.001
BMI (kg/m^2)	1.00 (0.61–1.64)	0.992	1.09 (0.64–1.87)	0.746
Goodness-of-fit (Hosmer–Lemeshow test)	χ^2=9.449, *df*=8	0.306	χ^2=5.191, *df*=8	0.062

CL_{CR} was estimated with the Cockcroft–Gault equation.
OR compares the CL_{CR} range against CL_{CR} >100 mL/min, which was the reference category.

≤100 mL/min and female gender were associated with target attainment for both antibiotics. In this analysis, the use of prolonged infusion was not significant, which emphasizes the fact that this altered method of administration is most effective in patients with higher levels of renal function.

These data suggest that clinicians need to be mindful of patients with elevated CL_{CR}, including ARC, which is associated with lower trough β-lactam concentrations.[29] As piperacillin and meropenem, like many other β-lactam antibiotics, are hydrophilic compounds and are eliminated by glomerular filtration, ARC is likely to be a highly important covariate for dosing. This hypothesis was confirmed by a study by Udy *et al*.[29] that showed that patients with ARC were significantly more likely to have lower β-lactam trough concentration.

There are some limitations to this study. First, the study retrospectively evaluated previous TDM data, and we used only one plasma antibiotic concentration on one day of therapy, which was not consistent across the patients. This approach may have reduced the reliability of the results because the effects of non-steady-state PK could not be tested. This lack of testing may have made it less likely that weight and/or BMI could be shown to be associated with PK/PD target attainment, as their effects are likely to be more prominent on antibiotic volume of distribution. However, the broad inclusion criteria of the sample may have mitigated this limitation. Second, the exact timing of the blood sample collections could not be guaranteed, which may have reduced the accuracy of the concentration results. Third, there were numerous differences in patient characteristics between the obese and non-obese patients, whereby the obese patients were generally younger and male with a higher calculated CL_{CR}, all factors associated with lower antibiotic concentrations.[29] The effect of these different patient characteristics on PK/PD target attainment was quantifiable in the logistic regression analysis. Fourth, the number of patients receiving prolonged infusion of piperacillin in the non-obese group was larger than that in the obese group, which may affect the representativeness of the data, although we believe that the multivariate analysis approach should overcome any potential confounding introduced by having unequally sized groups. Finally, the Cockcroft–Gault equation was used in this study to estimate the CL_{CR}, and although this may lead to a less accurate estimation of renal function, it is still commonly used clinically to guide therapy.

Conclusions

The combination of critical illness and obesity can produce physiological changes that cause significant alterations in renal function and volume of distribution, which can affect concentrations of β-lactam antibiotics. We found that critically ill obese patients who have a CL_{CR} >50 to ≤100 mL/min have lower trough concentrations for piperacillin when the antibiotic is administered by prolonged infusion. Consequently, critically ill obese patients should receive dosing regimens that aim to achieve therapeutic concentrations that increase the likelihood of clinical cure. For some patients receiving piperacillin in particular, it appears that a weight-based dose may be needed, although this finding was not significant in our logistic regression analysis. However, we are aware that this is a retrospective study, and we believe strong conclusions are possible only after a prospective study.

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Transparency declarations

None to declare.

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