Repeated Piperacillin-Tazobactam Plasma Concentration Measurements in Severely Obese Versus Nonobese Critically Ill Septic Patients and The Risk of Under and Overdosing

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Objective: Obesity and critical illness modify pharmacokinetics of antibiotics, but piperacillin-tazobactam continuous IV infusion pharmacokinetics has been poorly studied in obese critically ill patients. We aimed to compare pharmacokinetics of piperacillin in severely obese and nonobese patients with severe sepsis or septic shock. We hypothesized that plasma concentration variability would expose the critically ill to both piperacillin under and overdosing.

Methods: Prospective comparative study. Consecutive critically ill severely obese (body mass index, $> 35\,kg/m^2$) and nonobese patients (body mass index, $< 30\,kg/m^2$) were treated with 16 g/2 g/24 hr continuous piperacillin-tazobactam infusion. Piperacillin plasma concentration was measured every 12 hours over a 7-day period by high-pressure liquid chromatography. Unbound piperacillin plasma concentration and fractional time of plasma concentration spent over 64 mg/L (4-fold the minimal inhibitory concentration for *Pseudomonas aeruginosa*) were compared between the two groups. We performed 5,000 Monte Carlo simulations for various dosing regimens and minimal inhibitory concentration and calculated the probability to spend 100% of the time over 64 mg/L.

Results: We enrolled 11 severely obese and 12 nonobese patients and obtained 294 blood samples. We did not observe a statistically significant difference in piperacillin plasma concentrations over time between groups. The fractional time over 64 mg/L was 64% (43–82%) and 93% (85–100%) in obese and nonobese patients, respectively, $p = 0.027$ with intra- and intergroup variability. Five nonobese and two obese patients experienced potentially toxic piperacillin plasma concentrations. When 64 mg/L was targeted, Monte Carlo simulations showed that 12 g/1.5 g/24 hr was inadequate in both groups and 16 g/2 g/24 hr was adequate only in nonobese patients.

Conclusion: Using a conventional dosing of 16 g/2 g/24 hr continuous infusion, obese patients were more likely than nonobese patients to experience piperacillin underdosing when facing high minimal inhibitory concentration pathogens. The present study suggests that piperacillin drug monitoring might be necessary in the sickest patients who are at the highest risk of unpredictable plasma concentration exposing them to overdose, toxicity, underdosing, and treatment failure.

Key Words: Monte Carlo simulation; obesity; piperacillin-tazobactam; population pharmacokinetic; septic shock

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The frequency of obesity is increasing worldwide and may affect up to 30% of critically ill patients (1) leading to multiple challenges in the care of this particular population (2–4).

TABLE 1. Demographic and Outcome Characteristics

Variable	Nonobese ($n = 12$)	Obese ($n = 11$)	p
Age (yr)	67 ± 15	61 ± 10	0.25
Male, *n* (%)	7 (58)	3 (27)	0.15
Total body weight (kg)	67 ± 11	125 ± 38	< 0.01
Body mass index (kg/m^2)	23 ± 4	45 ± 12	< 0.01
Past medical history, *n* (%)			
Alcohol abuse	1 (8)	1 (9)	0.94
Tobacco use	1 (8)	5 (45)	0.06
Diabetes mellitus	2 (17)	3 (18)	0.92
Hypertension	6 (50)	6 (54)	0.83
Stage New York Heart Association III or IV heart failure	1 (8)	0	0.33
Stage 3 or above chronic kidney disease	3 (25)	1 (9)	0.33
Liver cirrhosis	1 (8)	0	0.33
Stage III or above chronic obstructive pulmonary disease	1 (8)	4 (36)	0.26
Active malignancy	2 (17)	1 (9)	0.59
Severity scores upon ICU admission			
Simplified Acute Physiology Score II	51 ± 16	46 ± 16	0.67
Sequential Organ Failure Assessment	9 ± 5	8 ± 4	0.66
Knaus scale			
A	0	1 (9)	0.34
B	7 (67)	4 (36)	0.31
C	5 (33)	5 (45)	0.86
D	0	1 (9)	0.34
Reason for ICU admission			
Septic shock	11 (92)	8 (73)	0.23
Severe sepsis	1 (8)	2 (18)	0.48
Acute respiratory failure	0 (0)	1 (9)	0.28
Albumin blood level (g/dL) upon ICU admission	26.5 (24.5–29.5)	31 (24–33)	0.38
Estimated glomerular filtration rate (mL/min/1.73m^2) upon ICU admission	29.6 (20.8–49.3)	43.7 (29.2–62.6)	0.48
Renal replacement therapy during the ICU stay, *n* (%)	2 (17)	1 (9)	0.58
Clinical response			0.08
Cure	6 (50)	7 (64)	
Failure	5 (42)	1 (9)	
Indeterminate	1 (8)	3 (27)	
Site of infection			
Lung	4 (33)	6 (55)	0.33
Intra-abdominal	6 (50)	3 (27)	0.53
Blood	2 (17)	0	0.16
Urinary tract	0	1 (9)	0.34
Endocarditis	0	1 (9)	0.34

(Continued)

TABLE 1. *(Continued)*. Demographic and Outcome Characteristics

Variable	Nonobese ($n = 12$)	Obese ($n = 11$)	p
Microbiology	9 (75)	9 (91)	0.33
Enterobacteriaceae	7 (58)	2 (18)	0.05
Citrobacter freundii	0	0	1
Enterobacter aerogenes	0	0	1
Enterobacter cloacae	1 (8)	0	0.33
Escherichia coli	4 (33)	1 (9)	0.17
Klebsiella pneumoniae	1 (8)	1 (9)	0.9
Morganella morganii	1 (8)	0	0.33
Proteus mirabilis	0	0	1
Other Gram-negative bacteria	2 (17)	3 (27)	0.82
Burkholderia species	1 (8)	0	0.33
Haemophilus influenzae	0	1 (9)	0.34
Pseudomonas aeruginosa	1 (8)	2 (18)	0.51
Stenotrophomonas maltophilia	0	0	1
Gram-positive bacteria	1 (8)	5 (45)	0.05
Enterococcus faecalis	0	2 (18)	0.16
Staphylococcus aureus	0	2 (18)	0.16
Coagulase-negative *Staphylococcus*	0	0	1
Streptococcus species	1 (8)	1 (9)	0.9

Values are presented as mean values ± SD. The Knaus chronic health status score describes health status prior to ICU admission with: A, normal health status; B, moderate activity limitation; C, severe activity limitation due to chronic disease; and D, bedridden patient. Chronic obstructive pulmonary disease severity was assessed using the Global Initiative for Chronic Obstructive Lung Disease staging. Chronic kidney disease severity was stratified according to Kidney Disease, Improving Global Outcomes guidelines.

Obese patients are also more frequently affected by severe sepsis (5). One of the main available interventions among the few initiatives that have been associated with improved outcomes in septic shock is shortening the time from onset of sepsis symptoms to administration of adequate antibiotics (6–8). Because of its broad spectrum, bactericidal action, and well-tolerated drug profile, piperacillin-tazobactam (PTZ) is one of the most prescribed antibiotics for severe infections in the ICU.

Both obesity and septic shock are associated with an increase in volume of distribution of β-lactams (9). The renal clearance of β-lactams might be elevated if the patient demonstrates a supranormal glomerular filtration rate that is common in obese patients (10) and at the early stage of sepsis (11). Renal clearance might also be decreased because of obesity-associated chronic kidney failure or secondary to sepsis-related acute kidney injury (10). Therefore, plasma concentration and half-life might be highly unpredictable in obese critically ill septic patients exposing them to both under and overdosing. Compared to bolus infusion, extended and/or continuous PTZ infusion lead to a higher probability of pharmacokinetics (PK) target attainment (12, 13) and possibly have a positive impact on outcome (14). However, to date, the pharmacodynamic and pharmacokinetic (PKPD) profile of continuous PTZ regimen in obese and nonobese critically ill patients has not been specifically compared.

This prospective study aimed to compare the piperacillin (PIP) PKPD in a homogenous population of critically ill severely obese and nonobese patients with severe sepsis or septic shock treated by a continuous 16 g/2 g/24 hr PTZ infusion. We hypothesized that obese patients would be more likely to experience PIP underdosing than nonobese patients. We also hypothesized that both groups would present plasma PIP variability suggesting the need for PIP therapeutic drug monitoring in the ICU setting.

METHODS

Patients

Between February 2012 and May 2013, we conducted a prospective comparative study in a 16-bed medical and surgical ICU (ClinicalTrial NCT01517815). All consecutive patients over 18 years old presenting with severe sepsis or septic shock needing a broad-spectrum antibiotic therapy with PTZ and with an expected ICU stay of more than or equal to 5 days were eligible for inclusion. Severe sepsis and septic shock were diagnosed

using Surviving Sepsis Campaign criteria (8). Patients were divided into two groups considering their body mass index (BMI) (BMI [kg/m^2] = weight [kg]/height^2 [m^2]): a nonobese group for BMI less than 30 kg/m^2 and a severely obese group for BMI greater than 35 kg/m^2. Daily weight was obtained using the ICU bed scale. Exclusion criteria included a history of allergy to penicillins or documented resistance to PTZ. At inclusion, demographic variables, severity scores, laboratory values (creatinine, albumin, and glomerular filtration rate), and the site of infection were collected. "Kidney failure" was defined as a glomerular filtration rate of 30 mL/min or below (15). In accordance with the current guidelines (16), criteria for continuous venovenous hemofiltration initiation included both metabolic emergencies and persistent acute kidney injury (Acute Kidney Injury Network 2–3) despite resuscitation for at least 12 hours. The current study was approved by the hospital medical-ethics committee (EudraCT number: 2011-005233-38) and was carried out in concordance with The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines for Good Clinical Practice (17). Informed consent was obtained from every patient or his/her next-of-kin if the patient was unable to provide informed consent. We evaluated the clinical response to PTZ at the test-of-cure visit scheduled at the end of drug therapy. Clinical responses were defined as follows (18): 1) cure, the complete resolution or significant improvement of signs or symptoms of the initial infection, such that additional antibacterial therapy was not required; 2) failure, death related to the initial infectious process, persisting or recurrent infection of the initial septic site, or the need for additional antibacterial therapy for ongoing symptoms of the initial infection; and 3) indeterminate, evaluation could not be done for any reason, or extenuating circumstances prevented from classification as cure or failure.

Design of the Study

Patients received a 1-hour PTZ 4 g/0.5 g IV bolus followed by a continuous drip of PTZ 16 g/2 g diluted in 48 mL sterile water and administered via electric infusion pump at a 2 mL/hr rate.

Venous blood samples (5 mL) were collected as follows: a first sample was collected 1 hour after the end of the 4/0.5 g bolus and then samples were collected every 12 hours over a 7-day period for a maximum of 15 samples for each patient. Blood samples were immediately centrifuged at 2,500 rpm for 10 minutes, and serum was stored at –80°C until analysis. Serum samples were transported on dry ice to the Laboratory of Clinical Pharmacokinetics and Clinical Pharmacy (Bordeaux, France) for measurement of both free PIP and tazobactam (TAZ) concentrations. Sampling was stopped in case of discharge from the ICU, early end of treatment, or death before the end of study. Clinicians were blinded to the results at the time of clinical assessment and during the antibiotic course.

PIP and TAZ Assay

Unbound fractions of PIP and TAZ in serum were measured as previously described (19). Briefly, high-performance liquid chromatography was used with a gradient system, acetonitrile from 5% (TAZ) to 25% (PIP) for mobile phase adjusted at pH equals to 6.5 with a solution of phosphate buffer. PIP and TAZ in serum were quantified after adding 1 mL of the sample with 20 µL of trifluoroacetic acid. The lower limit of detection of PIP was 0.25 µg/mL in serum, and linearity was validated from 0.25 to 500 µg/L. All results were within 5% at all levels, and the assay was validated and conducted according to criteria specified by the U.S. Food and Drug Administration guidance on bioanalysis (20).

PK Analysis

Total body clearance (TCL) was calculated as the ratio between the maintenance dose administration rate (K0) over the steady-state PIP concentrations (Css) using the formula TCL = K0/Css. The time to reach the steady state was 3.5–5-fold the halftime of elimination starting 12 hours after the continuous infusion. Css concentrations heterogeneity are presented as mean and SDs and coefficient of variation (CV%) (SD over mean) for each patient.

Monte Carlo Simulations

Pharmacodynamic exposures were modeled for PIP by Monte Carlo simulations (n = 5,000) using R software (R version 2.15.2; The R Foundation for Statistical Computing; https://www.r-project.org). Three PTZ dosing regimens were simulated: 12 g/1.5 g/24 hr, 16 g/2 g/24 hr, and 20 g/2.5 g/24 hr in obese (BMI, > 35 kg/m^2) and nonobese patients (BMI, < 30 kg/m^2). Similarly to other β-lactams, the most important PK variable predicting bacteriological and clinical efficacy for PIP is the fractional amount of time spent with a serum concentration above a specific minimal inhibitory concentration (MIC). For each dosing regimen and BMI group, we calculated the probability of target attainment to spend more than 100% of the dosing interval over specific MICs (16, 32, and 64 mg/L).

Endpoints

The endpoints of the present study were the steady-state PK parameters of PIP, which were compared between obese and nonobese critically ill patients hospitalized for severe sepsis or septic shock in the ICU. We described the pharmacodynamics of PIP by calculating the probability of target attainment at different MICs and different PTZ dosing.

Statistical Analysis

The results are expressed as mean ± SD or median ± interquartile range (25–75th percentiles) or number and percentage and compared between nonobese and obese patients using Student, Mann-Whitney U, or chi-square tests according to the distribution of the variables. Because of the repeated measures, a generalized mixed model was used to model the concentration-time profiles (the multivariate model was selected with a stepwise procedure). Because the Sequential Organ Failure Assessment (SOFA) score was a significant component of the population, the model included the time and SOFA score as dependent variables. The Pearson correlation coefficient was used to assess the relationship between clearance, weight, and BMI. A multivariate analysis assessed whether BMI, measured creatinine clearance ([urine creatinine concentration × urine output]/[plasma creatinine concentration]), and SOFA score

TABLE 2. Pharmacokinetic Variables in Obese and Nonobese Critically Ill

Variable	PIP Concentration (mg/L)	PIP CV (%)	PIP Clearance (L/h)	TAZ Concentration (mg/L)	TAZ CV (%)	PIP Over TAZ Ratio
Severely obese						
Patient 1	55.83 ± 27.79	49.78	49.77	6.50 ± 3.12	47.97	8.6
Patient 2	66.47 ± 19.31	29.05	29.04	21.61 ± 4.07	18.86	3.1
Patient 3	172.27 ± 39.60	22.99	22.99	57.48 ± 13.88	24.14	3.0
Patient 4	75.06 ± 18.15	24.18	24.18	14.53 ± 3.54	24.36	5.2
Patient 5	89.58 ± 19.11	21.34	21.34	28.93 ± 6.90	23.83	3.1
Patient 6	57.17 ± 29.89	52.28	52.28	9.90 ± 9.55	96.51	5.8
Patient 7	64.05 ± 12.37	19.31	19.31	20.93 ± 12.56	59.99	3.1
Patient 8	82.45 ± 31.08	37.70	37.70	44.63 ± 11.79	26.41	1.8
Patient 9	28.86 ± 10.01	34.68	34.68	11.09 ± 3.13	28.26	2.6
Patient 10	176.01 ± 66.26	37.65	37.65	37.75 ± 10.73	28.42	4.7
Patient 11	59.61 ± 15.27	25.61	25.61	15.36 ± 6.18	40.25	3.9
Nonobese						
Patient 1	47.57 ± 14.71	28.81	42.04	9.45 ± 1.50	15.87	5.0
Patient 2	175.44 ± 55.03	31.37	11.40	37.63 ± 18.17	48.29	4.7
Patient 3	84.54 ± 21.34	25.24	23.66	22.93 ± 9.91	43.21	3.7
Patient 4	148.46 ± 30.04	20.23	13.47	37.30 ± 6.13	16.44	4.0
Patient 5	245.35 ± 31.73	12.93	8.15	89.3 ± 27.34	30.62	2.7
Patient 6	283.27 ± 63.82	22.53	7.06	53.15 ± 12.43	23.38	5.3
Patient 7	141.00 ± 52.51	37.24	14.18	42.38 ± 15.85	37.38	3.3
Patient 8	86.31 ± 31.28	36.24	23.17	43.19 ± 11.94	27.65	2.0
Patient 9	112.90 ± 17.13	15.17	17.71	41.00 ± 6.08	14.82	2.8
Patient 10	88.51 ± 21.41	24.19	22.60	25.35 ± 11.64	45.94	3.5
Patient 11	95.94 ± 24.14	25.16	20.85	37.09 ± 5.31	14.32	2.6
Patient 12	79.47 ± 9.77	12.29	25.17	19.14 ± 4.09	21.35	4.2
Severely obese	84.31 ± 47.14	32.23 ± 11.25	23.72 ± 42.43	24.43 ± 16.15	38.09 ± 22.97	3.5 ± 2.9
Nonobese	140.11 ± 69.21	23.87 ± 8.58	14.27 ± 28.90	40.77 ± 18.91	29.40 ± 12.64	3.4 ± 3.7
p	< 0.01	0.12	0.03	< 0.01	0.23	0.86

CV = coefficient of variation (%) (calculated as SD/mean), PIP clearance = piperacillin total body clearance, PIP concentration = piperacillin concentration at steady state, TAZ concentration = tazobactam concentration at steady state.

over time were associated with PIP plasma concentration and was included in the Monte Carlo simulation. We hypothesized that obese patients would present with plasma concentrations of PIP reduced by 50% compared with nonobese patients with a SD corresponding to a third of the expected concentrations in nonobese patients. We calculated that eight patients per group would be necessary to test our hypothesis with a one-tailed α risk of 5% and a β risk of 10%. Intention to treat statistical analysis was performed by the medical statistical department of the Montpellier University Hospital (NM), with R software (The R Foundation for Statistical Computing). A p value of less than 0.05 was considered statistically significant.

RESULTS

Patients

A total of 12 nonobese (BMI of 23 ± 4 kg/m^2) critically ill patients and 11 severely obese (BMI of 45 ± 12 kg/m^2) critically ill patients receiving PTZ for septic shock or severe sepsis were included in the study, and a total of 294 blood samples were collected (**Table 1**). Nine patients developed criteria for kidney failure, and three patients needed renal replacement therapy during their ICU stay (Table 1). Pneumonia and peritonitis were the two main sources of sepsis with a documented site of infection in 18 (79%) of the cases (Table 1; **supplemental material**, Supplemental Digital Content 1,

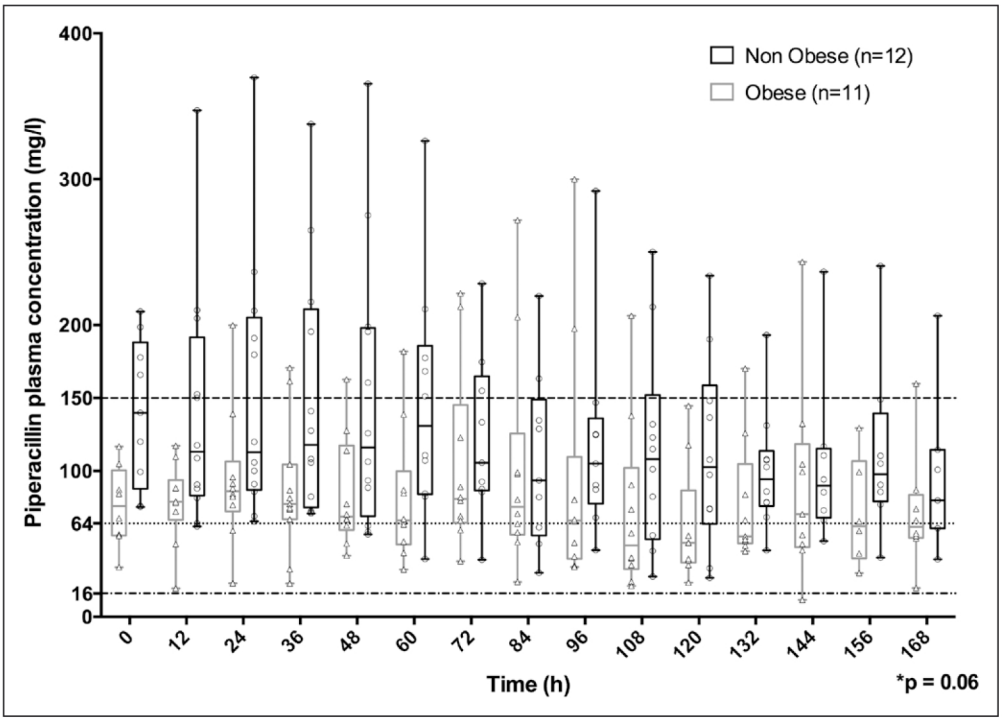

Figure 1. Piperacillin blood concentrations (median, quartiles, and individual values) over the 7-d study period for nonobese ($n = 12$) and severely obese ($n = 11$) patients. The *Pseudomonas aeruginosa* minimal inhibitory concentration breakpoint (16 mg/L), 4-fold the breakpoint (64 mg/L), and the potential piperacillin toxic concentration threshold (150 mg/L) are represented as *dashed lines*. Over the study period, piperacillin concentration was compared between the two groups of patients using a mixed logistic model, which took into account the Sequential Organ Failure Assessment (SOFA) severity score. *Between obese and nonobese patients over time, adjusted to SOFA score.

http://links.lww.com/CCM/C405; and **Supplemental 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/C406).

PK Analysis

Clearance for PIP almost doubled in obese compared to nonobese patients (**Table 2**) and was correlated with both total body weight ($p < 0.01$) and BMI ($p = 0.01$) but neither with ideal nor lean body weight. Using the continuous IV administration of 16 g/2 g/24 hr of PTZ regimen, no patient experienced a significant amount of time below the cutoff of 16 mg/L. The 150 mg/L threshold has been previously associated with neurotoxicity (21), and time spent above this threshold was observed in five nonobese and two obese patients (**Fig 1**). PIP plasma concentration variability was observed in both groups (Fig 1 and Table 2) but also in every patient with extreme values from 12 to 370 mg/L (**Fig. 2**, ***A*** and ***B***). Although raw PIP plasma concentrations were different among groups (Table 2), when time and repeated measures were considered, we did not observe a statistically significant difference in PIP plasma concentration (Fig 1). With no difference between groups, we observed a mean PIP concentration drop over time of 0.15 mg/L/hr (24 mg/L/wk) over the stay. Two nonobese patients and one obese patient needed continuous hemofiltration and PIP concentration ranged in these patients from 40 to 370 mg/L (Fig. 2, *A* and *B*). Creatinine clearance was measured in 27 occasions upon the physician's request. PIP concentration and creatinine clearance were not statistically correlated (**Supplemental 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/C407). A multivariate analysis showed that BMI, measured creatinine clearance, and SOFA score over time were associated with PIP plasma concentration ($p < 0.01$). The PIP over TAZ ratio was not impacted by weight (Table 2). Using a mixed model to describe the concentration-time profiles with time and SOFA score as dependent variables, median time spent over 64 mg/L was 93% (85–100%) in nonobese and 64% (43–82%) in obese patients ($p = 0.027$) (Fig. 1). When four times the breakpoint of *Pseudomonas aeruginosa* was considered (64 mg/L), eight obese (72%) and five (42%) nonobese patients experienced time below 64 mg/L (Fig. 2, *A* and *B*).

Monte Carlo Simulation

Table 3 presents the probability of target attainment of spending 100% of the time over MIC breakpoints of 16, 32, and 64 and the toxic cutoff of 150 mg/L with different dosing regimens for critically ill septic obese and nonobese patients. A PTZ regimen of 16 g/2 g/24 hr was appropriate for a target MIC of up to 64 mg/L except in obese patients. The 12 g/1.5 g/24 hr PTZ regimen was associated with a low probability of reaching the target when 64 mg/L was considered as a cutoff, independent of the weight of the patients.

DISCUSSION

In this prospective comparative study, we observed that despite a continuous IV infusion, PIP plasma PK levels showed intra- and interindividual variability over the 7-day study period in both severely obese and nonobese critically ill, thus exposing patients to both underdosing and potentially toxic PIP concentrations. We did not observe a statistically significant difference in PIP plasma concentration over time between groups. However, severely obese patients were more likely to experience PIP underdosing when assuming a plasma target of 64 mg/L, which is four times the breakpoint for *P. aeruginosa*. This study favors PIP therapeutic drug monitoring in critically ill patients and especially in obese critically ill who face unpredictable PIP plasma concentrations.

Obesity is affecting a growing population in the ICU, but few studies have evaluated PIP PK in obese critically ill patients

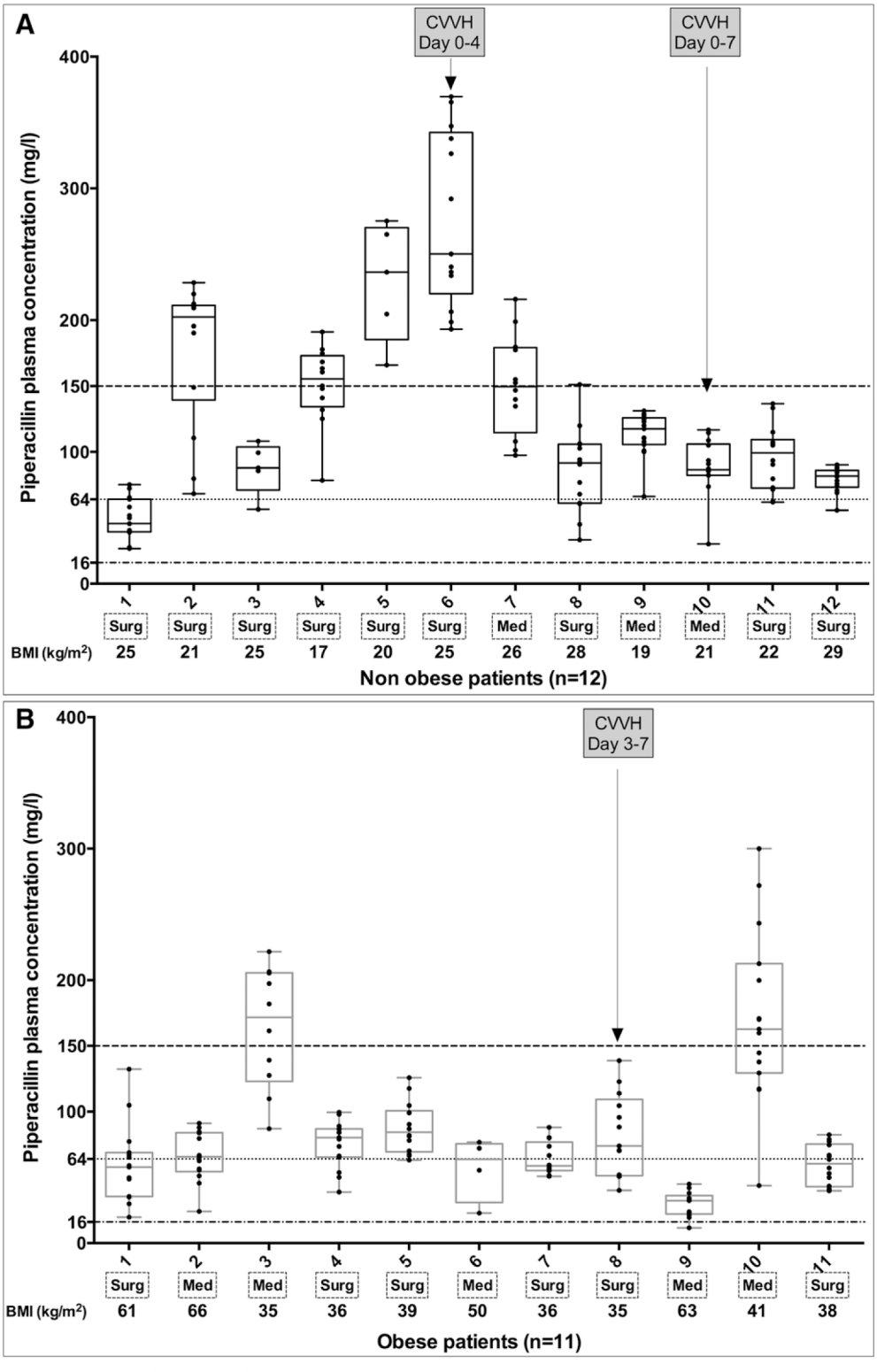

Figure 2. *Box plots* showing all piperacillin plasma concentrations among the 12 individual nonobese patients over the 7-d study period. *P. aeruginosa* minimal inhibitory concentration breakpoint (16 mg/L), 4-fold the breakpoint (64 mg/L), and the potential piperacillin toxic concentration threshold (150 mg/L) are represented as *dashed lines*. Continuous venovenous hemofiltration (CVVH) was used from day 0 to day 4 in patient 6 and from day 0 to day 7 in patient 10. Med = medical admission, Surg = surgical admission as defined by surgery in the 48 hr before ICU admission.

(22–24). These studies have either compared critically ill or noncritically ill obese patients (22), described PIP PK in nonsevere critically ill obese patients (23) or described PIP PK with only one plasma concentration measurement after a 30-min PTZ 4 g/0.5 g bolus (24). A recent post hoc analysis of a large dataset that combined several PTZ doses, intermittent and continuous IV administrations, and total and unbound PIP concentration measurements reported that obesity and altered renal clearance were associated with a high frequency of low PIP plasma concentration (25). Our study is in line with these results but was specifically designed to assess both intergroup and intragroup over time variability. The present study design allowed the prospective comparison of PIP PK between nonobese and obese critically ill all treated with PTZ for severe sepsis or septic shock over a 7-day period with a mean of 12 time points per patient.

Despite the presence of nine patients with criteria for kidney failure, PIP CL was three to five times faster than previously reported in critically obese patients (22, 23) in line with the variability of renal clearance in the critically ill. Nonrenal elimination of PIP by high fluid output drains in some of the surgical patients may also have occurred (26). The PIP over TAZ ratio was not different between groups but higher than reported in obese critically ill (22) or in critically ill needing renal replacement therapy (27) suggesting that PIP monitoring alone would reflect TAZ concentration kinetics. A higher ratio of PIP over TAZ plasma concentration has been sparsely linked to a better efficacy in experimental models (28).

In the present study, the continuous infusion was associated with a dramatic PIP concentration variability between groups, over time and in each patient group. Furthermore,

PIP concentration dropped by 24 mg/L/wk suggesting that some patients would have needed extra PTZ bolus. On the other hand, some patients experienced very high plasma concentrations, above the supposed toxic cutoff of 150 mg/L which might be associated with renal and neurologic toxicities in large datasets (29). Although PIP plasma concentration variability with discontinuous infusion has been reported in noncritically ill (30) and critically ill patients (21, 31, 32), the continuous infusion regimen should theoretically mitigate the plasma concentration variability. In the present study, a multivariate model showed that the SOFA score and creatinine clearance were associated with PIP concentration kinetic over time. Alteration in PK parameters stability over time and extra renal CL may also have influenced PIP concentrations over the study period. PIP plasma concentration was constantly above the *P. aeruginosa* breakpoint of 16 mg/L. Although the classical target for penicillin is to maintain a concentration above MIC for 40–50% of the time (33), recent studies reported that higher drug over MIC ratio and longer time above MIC might be necessary to ensure clinical and microbiological response (34–36). In the present study, when considering a 4-fold breakpoint for *P. aeruginosa* (64 mg/L) during 100% of the time period, obese patients were more likely to experience underdosing than nonobese patients.

This study has a number of limitations. First, our sample size was relatively small but comparable to other studies in the field (22, 23, 32, 37). Second, critical illness has been both associated with augmented renal clearance and impaired renal clearance and matching renal function between groups would have allowed more accurate comparison between groups. Not excluding patients needing renal replacement therapy might also have had an impact on drug concentration. However, our study attempted to reflect bedside management and reports unpredictable and highly variable concentrations in both groups. The present study was not designed to specifically address the relation between measured creatinine clearance and PIP plasma concentration. Third, we did not measure tissue concentrations, and any conclusions based on plasma concentrations must be interpreted with caution as PTZ penetration into tissues is also subject to variability (12, 36, 38). Finally, PTZ was infused with the same 4 g/0.5 g bolus and 16 g/2 g continuous regimen because we expected that dose adaptations based on weight and glomerular filtration rate would have been inadequate (36).

In conclusion, despite limitations related to kidney function and the small numbers of patients, our prospective study suggests that in nonobese but more particularly in severely obese critically ill patients, PIP plasma concentration varies over time, among groups, and also within each patient despite a continuous regimen of 16 g/2 g/24 hr. Although most of the patients spent more than 50% of the time above the *P. aeruginosa* breakpoint of 16 mg/L, half of them experienced very high concentrations. Monte Carlo simulations show that 12 g/1.5 g/24 hr was associated with the risk of underdosing when higher concentration over MIC was considered. The present study suggests that PIP drug monitoring might be necessary in the sickest patients who are at the highest risk of unpredictable plasma concentration exposing them to overdose, toxicity and underdosing and treatment failure.

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TABLE 3. Probability of Target Attainment for Specific Minimal Inhibitory Concentrations With Different Dosing Regimen of Piperacillin-Tazobactam in Monte Carlo Simulation

Targeted Minimum Inhibitory Concentration (mg/L)	Probability of Target Attainment (%)					
	PTZ 12 g/1.5 g/24 hr		PTZ 16 g/2 g/24 hr		PTZ 20 g/2.5 g/24 hr	
	Obese	Nonobese	Obese	Nonobese	Obese	Nonobese
16	90	100	100	100	100	100
32	88	100	91	100	100	100
64	21	65	44	98	75	100
150	0	8	12	27	18	42

PTZ = piperacillin-tazobactam.

The optimal target was to spend 100% of the time over breakpoints minimum inhibitory concentrations of 16, 32, and 64 mg/L.

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