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PHARMACOLOGY

Population Pharmacokinetics of Piperacillin in Sepsis Patients: Should Alternative Dosing Strategies Be Considered?

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ABSTRACT Sufficient antibiotic dosing in septic patients is essential for reducing mortality. Piperacillin-tazobactam is often used for empirical treatment, but due to the pharmacokinetic (PK) variability seen in septic patients, optimal dosing may be a challenge. We determined the PK profile for piperacillin given at 4 g every 8 h in 22 septic patients admitted to a medical ward. Piperacillin concentrations were compared to the clinical breakpoint MIC for *Pseudomonas aeruginosa* (16 mg/liter), and the following PK/pharmacodynamic (PD) targets were evaluated: the percentage of the dosing interval that the free drug concentration is maintained above the MIC (fT_{MIC}) of 50% and 100%. A two-compartment population PK model described the data well, with clearance being divided into renal and nonrenal components. The renal component was proportional to the estimated creatinine clearance (eCL_{CR}) and constituted 74% of the total clearance in a typical individual (eCL_{CR}, 83.9 ml/min). Patients with a high eCL_{CR} (>130 ml/min) were at risk of subtherapeutic concentrations for the current regimen, with a 90% probability of target attainment being reached at MICs of 2.0 (50% fT_{MIC}) and 0.125 mg/liter (100% fT_{MIC}). Simulations of alternative dosing regimens and modes of administration showed that dose increment and prolonged infusion increased the chance of achieving predefined PK/PD targets. Alternative dosing strategies may therefore be needed to optimize piperacillin exposure in septic patients. (This study has been registered at ClinicalTrials.gov under identifier NCT02569086.)

KEYWORDS augmented renal clearance, dosage optimization, piperacillin, population pharmacokinetics, sepsis

Appropriate empirical antibiotic therapy is crucial for reducing mortality in septic patients (1). Most hospitals worldwide use a standard fixed-dose regimen for treatment, but with numerous pharmacokinetic (PK) alterations being seen in this patient population (2), how do we know that this dose is right? Due to the pathophysiological changes associated with the septic process, antibiotic plasma concentrations are variable and hard to predict (3, 4). Optimal dosing and exposure can therefore be a challenge in septic patients, and standard antibiotic dosing regimens may result in subtherapeutic concentrations and therapeutic failure (5, 6). Appropriate dosing is also essential in order to maximize bacterial killing and minimize the development of antimicrobial resistance (7–9).

Piperacillin-tazobactam is a β-lactam–β-lactamase inhibitor combination with extended-spectrum antibacterial activity which is often used for empirical treatment of severe infections (10). The antibacterial activity is time dependent; i.e., the activity is related to the percentage of the dosing interval that the free drug concentration is maintained above the MIC (fT_{MIC}). By maximizing fT_{MIC}, the therapeutic impact increases and the risk of drug resistance development is reduced (7). For β-lactams, an

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TABLE 1 Patient characteristics[a]

Characteristic	Values
Median (IQR) age (yr)	57 (33, 76)
No. (%) of subjects who were:	
Male	12 (55)
Female	10 (45)
Median (IQR) body wt (kg)	76 (64, 82)
Median (IQR) plasma creatinine concn (μmol/liter)	97 (66, 132)
Median (IQR) plasma albumin concn (g/liter)	28 (24, 31)
eCL_{CR} (ml/min)	83.9 (46, 152)

[a]Data are for 22 patients. IQR, interquartile range; eCL_{CR}, estimated creatinine clearance, determined using the Cockcroft-Gault formula.

fT_{MIC} of at least 50% is associated with clinical efficacy (11); however, higher targets may be needed for a maximal bactericidal effect in critically ill patients (12, 13). By standard practice, piperacillin-tazobactam is administered as a bolus by intermittent administration (IA). Nevertheless, prolonged infusion, both extended infusion (IE) and continuous infusion (CI), has been suggested to optimize drug exposure and offers a PK advantage over IA, in that the T_{MIC} achieved with prolonged infusion is higher than that achieved with IA (14, 15).

Most β-lactams are primarily renally cleared, and there is consequently a relationship between creatinine clearance (CL_{CR}) and the β-lactam concentration-time course (16). In the early phase of critical illness, such as sepsis, an elevation of glomerular filtration is frequently seen, resulting in augmented renal clearance (ARC), defined as a CL_{CR} of $>$130 ml/min (17). ARC is mainly seen in younger patients and is associated with subtherapeutic antibiotic concentrations (18).

To prevent an adverse clinical outcome due to subtherapeutic concentrations, therapeutic drug monitoring (TDM) may be used to optimize the dose for an individual patient. It is increasingly used for β-lactams in patient populations with substantial PK variability (19).

When possible, an attempt to optimize the antibiotic dose according to patient characteristics (e.g., CL_{CR}) and PK knowledge for a given patient population should be applied, even before the first dose is administered. TDM may then be used as a tool to refine the dose when needed (20). Besides optimizing the antibiotic exposure, personalized therapy through TDM is recognized as a tool to reduce antimicrobial resistance development (21).

It has previously been shown that standard treatment with piperacillin-tazobactam (4 g/0.5 g) every 8 h (q8h) may result in subtherapeutic concentrations in septic shock patients admitted to an intensive care unit (ICU) (4). In the present study, we wanted to assess if there is a similar risk of subtherapeutic concentrations among less critically ill septic patients admitted to a general ward. In order to do this, we designed a prospective observational study with the aim to determine if intermittent administration of piperacillin-tazobactam q8h results in the recommended PK/pharmacodynamic (PD) target achievement in this patient population. By developing a population PK model, we assessed the current standard dose and simulated alternative dosing regimens and modes of administration.

RESULTS

Patient characteristics. Patient characteristics are shown in Table 1. A total of 22 patients were included in the study. Two patients fulfilled the criteria of severe sepsis at the time of inclusion. Their condition was stabilized within hours after treatment was initiated, and none of them developed septic shock. One patient developed septic shock and was transferred to an ICU. This patient was excluded from further monitoring. None of the remaining patients developed severe sepsis or septic shock. Four patients had augmented renal clearance (ARC) with an estimated creatinine clearance (eCL_{CR}) above 130 ml/min.

TABLE 2 The final parameter estimates from the current analysis[a]

Parameter	Parameter description	Estimated value from final model	% RSE (% SHR)
CL_{other} (liters/h)	Nonrenal clearance	2.23	36
$\theta_{eCL_{CR}\text{-}COV}$	eCL_{CR} covariate effect	0.0757	12
V_C (liters)	Volume of distribution of central compartment	12.4	8.3
Q (liters/h)	Compartmental clearance	3.54	3.0
V_P (L)	Volume of distribution of peripheral compartment	3.48	11
% CV for CL	Variability in clearance	29.7	13 (1.8)
% CV for ERR	Proportional residual error	11.5	21 (7.4)

[a]Total clearance was parameterized according to the formula $CL_{total,i} = (CL_{other} + \theta_{eCL_{CR}\text{-}COV} \cdot eCL_{CR,i}) \cdot e^{\eta i}$, where $CL_{total,i}$ is the individual total clearance (in millimeters per minute), CL_{other} is an estimated parameter describing nonrenal clearance (in liters per hour), $\theta_{eCL_{CR}\text{-}COV}$ is the estimated covariate effect, $eCL_{CR,i}$ is the individual eCL_{CR} (in millimeters per minute), and ηi is the deviation from the typical clearance in the individual. CV, coefficient of variation; CL, clearance; ERR, error; RSE, relative standard error; SHR, shrinkage.

Pharmacokinetic modeling. The parameter values for the final PK model are shown in Table 2. A visual predictive check based on the final model is shown in Fig. 1. The unbound piperacillin concentrations were best described by a two-compartment model with linear clearance from the central compartment. Differences between patients could be described by including an interindividual variability (IIV) term on elimination clearance. Inclusion of interoccasion variability (i.e., within-patient day-to-day variability) was not found to improve the model.

With regard to assessment of significant covariate relationships, inclusion of the patients' time-varying eCL_{CR} on elimination clearance improved the model fit (change in the objective function value [ΔOFV] = 32.3) and reduced the associated random variability in clearance, with the coefficient of variation (CV) decreasing from 48% to 30%. The best implementation was when a direct proportionality between clearance and eCL_{CR} was added to a constant clearance, as in $CL_{total,i} = (CL_{other} + \theta_{eCLCR\text{-}COV} \cdot eCL_{CR,i}) \cdot e^{\eta i}$, where $CL_{total,i}$ is the individual total clearance (in millimeters per minute), CL_{other} is an estimated parameter describing nonrenal clearance (in liters per hour), $\theta_{eCLCR\text{-}COV}$ is the estimated covariate effect, $eCL_{CR,i}$ is the individual eCL_{CR} (in millimeters per minute), and ηi is the deviation from the typical clearance in the individual. To exemplify, the total clearance in an individual with an eCL_{CR} of 40 ml/min would be 5.26 liters/h, 61% of the value in a typical individual (eCL_{CR} = 83.9 ml/min), without accounting for the random variability ($\eta i = 0$). As described earlier, the available eCL_{CR} values were carried backwards, reflecting the fact that the measured creatinine concentration is likely a reflection of kidney function in the time period preceding the

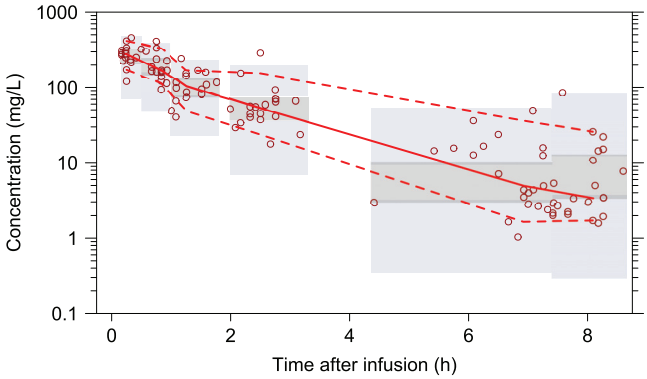

FIG 1 Visual predictive check based on the final model. Red circles, the observed concentrations in the current study; red solid line, the median of the observations; red dashed lines, 95th and 5th outer percentiles of the observations. The shaded area is derived from simulations from the final model, with the central dark gray area representing a 95% confidence interval for the median and the light gray areas representing the 95% confidence intervals for the 95th and 5th outer percentiles of the simulations.

TABLE 3 Number of subjects included in the analysis that were predicted to achieve the two PK/PD targets[a]

Regimen	No. of subjects predicted to achieve the following fT_{MIC} target/total no. of subjects evaluated (%)	
	50%	100%
IA at 4 g q6h	19/22 (86)	9/22 (40)
IA at 4 g q8h	15/22 (68)	4/22 (18)
IA at 4 g q12h	9/22 (41)	2/22 (9)
EI at 4 g q6h	22/22 (100)	14/22 (64)
EI at 4 g q8h	21/22 (95)	7/22 (32)
EI at 4 g q12h	14/22 (64)	2/22 (9)
CI at 16 g	22/22 (100)	22/22 (100)
CI at 12 g	22/22 (100)	22/22 (100)
CI at 8 g	22/22 (100)	22/22 (100)

[a]PK/PD, pharmacokinetic/pharmacodynamic; fT_{MIC}, percentage of the dosing interval that the free drug concentration is maintained above the MIC; IA, intermittent administration; EI, extended infusion; CI, continuous infusion.

measurement. No other statistically significant parameter-covariate relationships were identified.

For the current dosing regimen (IA at 4 g q8h), 15 of the patients (68%) were predicted to achieve a 50% fT_{MIC} and 4 patients (18%) were predicted to achieve a 100% fT_{MIC}, with results for the other regimens being shown in Table 3. Extended infusion (4 g every 6 h [q6h]) over 3 h would be sufficient to achieve a 50% fT_{MIC} in all patients, while continuous infusion (CI; 8 g) was needed in order to achieve a 100% fT_{MIC} with a mean steady-state concentration of 53.5 mg/liter (95% confidence interval, 38.8 to 68.2).

Predictions of the piperacillin 24-h profile for a patient with a CL_{CR} equal to the population median (83.9 ml/min) and a patient with a CL_{CR} equal to the highest value in the current population (174 ml/min) are depicted in Fig. 2. As by the model construction, plasma concentrations were higher for the patient with a median eCL_{CR}, though the peak concentrations following administration of an intravenous bolus were similar between the two patients. Assessing the eCL_{CR} covariate effect relative to the random variability (according to the equation presented above) showed that the 5th, 50th, and 95th percentiles of the clearances for a median patient were 5.26, 8.58, and 14.0 liters/h, respectively. Comparing these values to those for patients with eCL_{CR}s of 40 ml/min (5th, 50th, and 95th percentile clearances, 3.22, 5.26, and 8.56 liters/h) and 174 (5th, 50th, and 95th percentile clearances, 9.44, 15.4, and 25.1 liters/h), some degree of overlap due to the random variability in clearance can be seen.

Simulations. The probability of target attainment (PTA) curves, shown in Fig. 3, were constructed as a function of the MIC. To handle the included covariate effect, the values of eCL_{CR} were sampled from a normal distribution on the basis of the included patients (a median of 83.9 ml/min and a standard deviation (SD) of 45.5 ml/min with truncation at 20 and 180 ml/min). The difference in PTA between a 50% fT_{MIC} and a 100% fT_{MIC} for CI was predicted to be negligible (Table 3), and the PTA for a pathogen with an MIC equal to 16 mg/liter was 100% for all simulated dosing regimens. However, the PTA for IA and EI were generally much lower. As seen in Table 4, for piperacillin administered by IA at 4 g q8h, the PTA for a pathogen with an MIC equal to 16 mg/liter was 70.2% and 18.3% for a 50% fT_{MIC} and a 100% fT_{MIC}, respectively. This is far below the commonly accepted 90% target. The maximum MIC for a pathogen resulting in a 100% fT_{MIC} was 0.50 mg/liter.

The PTA as a function of the MIC for three different categories of eCL_{CR} is depicted in Fig. 4 and illustrates the impact of eCL_{CR} on piperacillin concentrations. For a pathogen with an MIC of 16 mg/liter, the standard dose of piperacillin of 4 g q8h resulted in target attainment below the accepted 90% target for patients with a CL_{CR} above 60 ml/min. Patients with a CL_{CR} above 130 ml/min were at great risk of subtherapeutic concentrations. For these patients, the probabilities of achieving a 50% fT_{MIC} and a 100% fT_{MIC} were 25% and 0%, respectively.

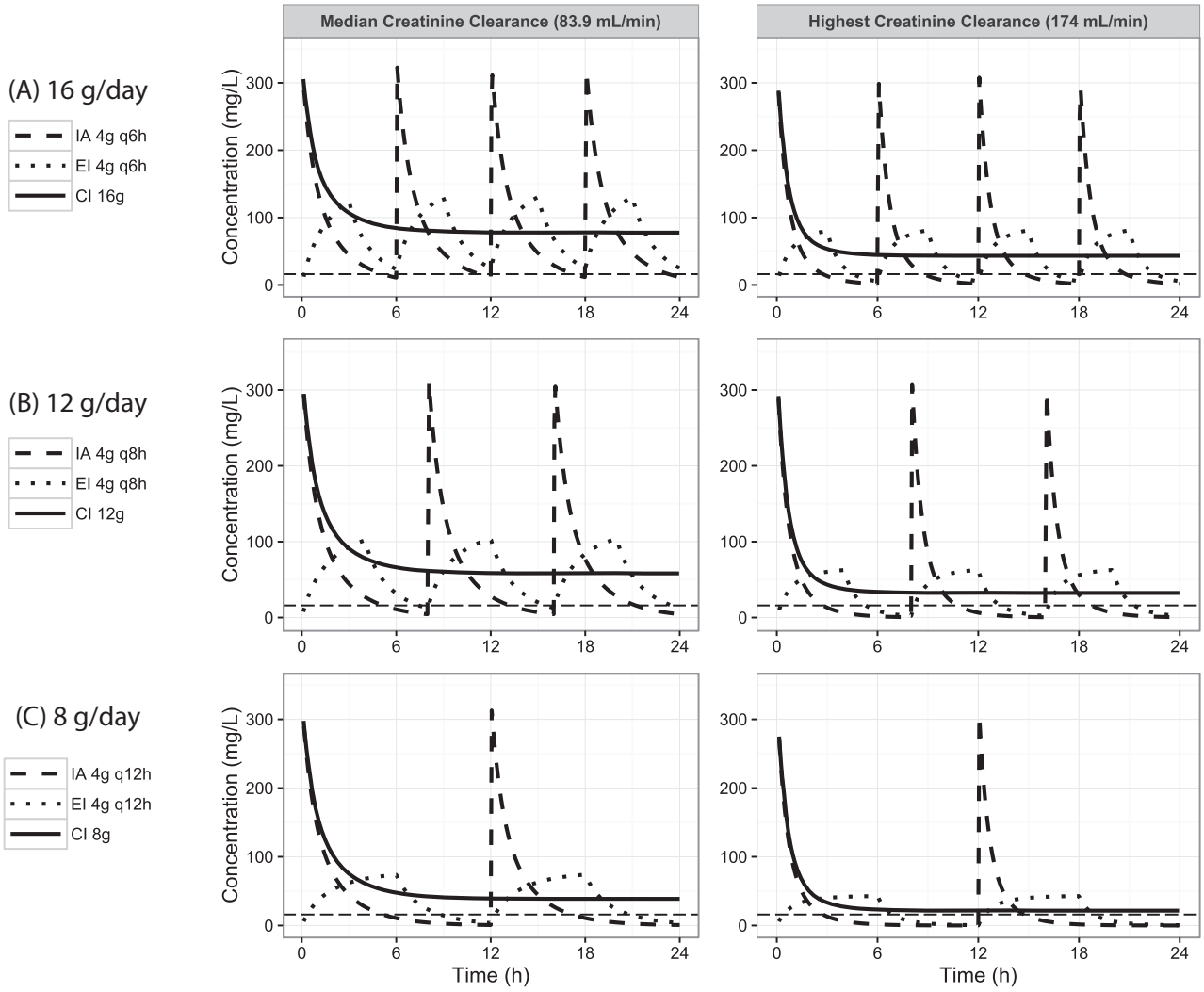

FIG 2 Predictions from the model for nine dosing regimens with a total administration of 16 g (A), 12 g (B), or 8 g (C) over 24 h for the median (left) and highest (right) creatinine clearances. Horizontal dashed lines, an MIC of 16 mg/liter. Continuous infusion was initiated with a loading dose of 4 g. IA, intermittent administration; EI, extended infusion; CI, continuous infusion.

DISCUSSION

Appropriate antibiotic dosing, initiated at an early stage, may be a challenge in septic patients due to the many PK alterations seen in this patient population. To address this issue, we developed a population PK model to assess the piperacillin PK profile in septic patients admitted to a general medical ward. Our results demonstrate that piperacillin at 4 g q8h administered as an intermittent infusion may result in subtherapeutic concentrations and that patients with augmented renal clearance are especially at risk. Furthermore, simulations based on the developed model show that prolonged infusion and the dose increment increase the chance of PK/PD target achievement.

Our data showed that piperacillin follows two-compartmental disposition kinetics and is eliminated by a linear process related to the individual patient's kidney function (determined by eCL_{CR}). A sampling strategy was developed on the basis of optimal design theory, which allowed the use of sparse sampling. The nonlinear mixed-effect analysis approach draws full advantage of the distribution of sampling times among patients, as all samples complement each other and aid in determining the individual's exposure to piperacillin. Nonlinearity in elimination mechanisms could not be estab-

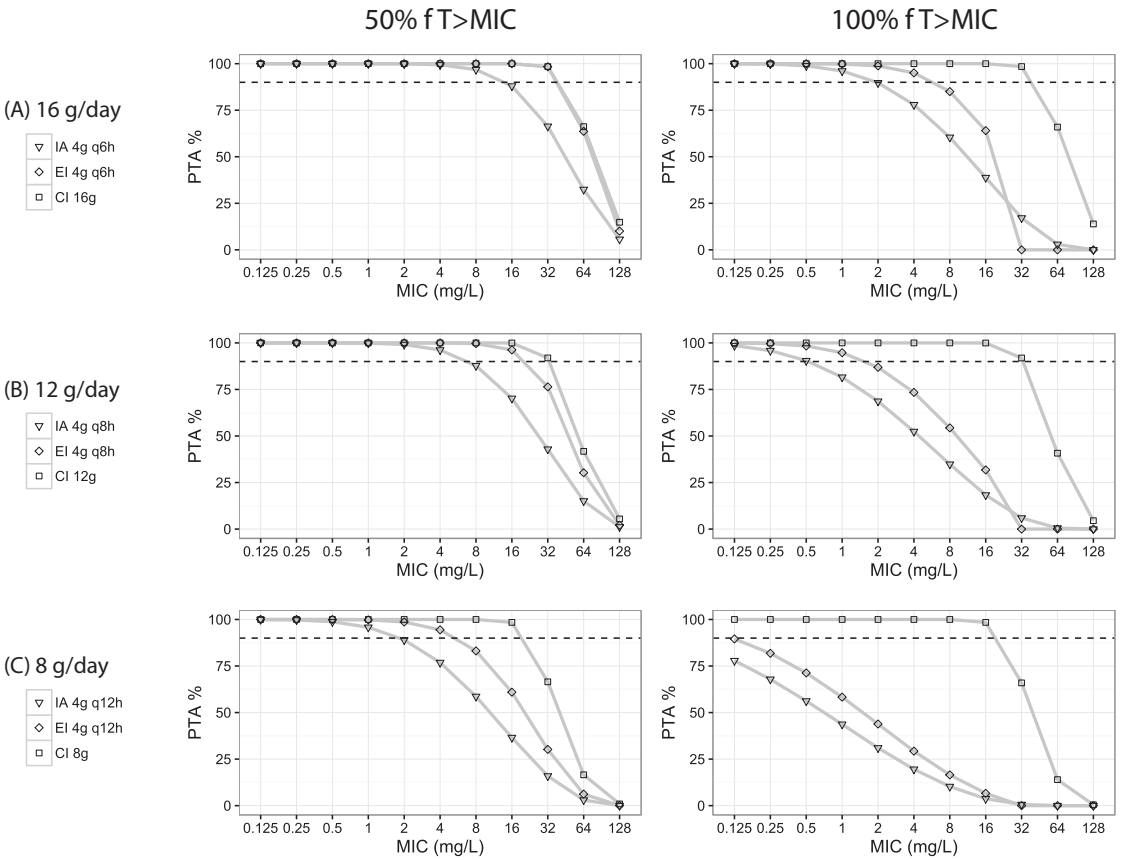

FIG 3 Probability of target attainment (PTA) for each of the nine regimens using the final model and a distribution of creatinine clearance values. The graphs indicate the total administration of 16 g (A), 12 g (B), or 8 g (C) as intermittent administration (IA), extended infusion (EI), or continuous infusion (CI). Dashed lines, 90% of the simulated patients reached the specified target; fT_{MIC}, the percentage of the dosing interval that the free drug concentration is maintained above the MIC.

lished on the basis of the collected data, although such a mechanism has been suggested in one previous study in healthy volunteers and was supported by the collection of urine (22). However, that study did not include a covariate effect of eCL_{CR} and further concluded that the nonlinearity has a limited impact on interpretation of PTA curves over a dose range of 6 to 18 g. In our study, the description of elimination was separated into renal and nonrenal components, with the renal component being scaled in proportion to the patient's eCL_{CR}. For the typical subject, renal elimination

TABLE 4 PTA for each of the nine regimens for MICs of 16 mg/liter and the MIC value at which PTA is predicted to be 90%[a]

Regimen	PTA (%) of the following for MIC of 16.0 mg/liter:		MIC (μg/ml) for PTA of 90% for:	
	50% fT_{MIC}	100% fT_{MIC}	50% fT_{MIC}	100% fT_{MIC}
IA at 4 g q6h	88.0	38.8	14.4	2.0
IA at 4 g q8h	70.2	18.3	7.0	0.5
IA at 4 g q12h	36.6	3.7	1.9	<0.125
EI at 4 g q6h	100	64.0	44.0	6.1
EI at 4 g q8h	96.2	31.8	22.3	1.6
EI at 4 g q12h	60.9	6.6	5.6	<0.125
CI at 16 g	100	100	44.5	44.5
CI at 12 g	100	100	33.7	33.5
CI at 8 g	98.4	98.4	22.2	22.2

[a]IA, intermittent administration; EI, extended infusion; CI, continuous infusion; fT_{MIC}, percentage of the dosing interval that the free drug concentration is maintained above the MIC; PTA, probability of target attainment.

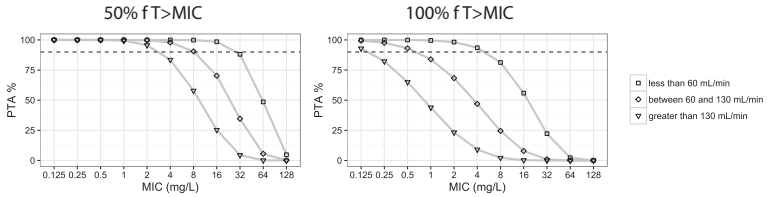

FIG 4 Probability of target attainment (PTA) for intermittent administration (IA) at 4 g q8h using the final model and a distribution of creatinine clearance values split into three empirical categories. Dashed lines, PTA of 90%; fT_{MIC}, the percentage of the dosing interval that the free drug concentration is maintained above the MIC.

would account for approximately 74% of the total clearance, similar to a mean value for urinary recovery of 72% reported previously in healthy volunteers (23). Comparing our results to those obtained with a previously established model, the volume of distribution of the central compartment was higher for septic patients (12.4 liters) than for patients with septic shock (7.3 liters), resulting in lower concentrations for a similar administered dose (4). The same was evident for clearance, which was almost twice as high for a typical septic patient (8.58 liters/h) as for a septic shock patient (3.6 liters/h), with the associated random variability being lower.

β-Lactam antibiotics are predominantly renally cleared; thus, renal function affects plasma concentrations (24). This relationship is illustrated in the 24-h pharmacokinetic profile predictions (Fig. 2). An increase in eCL_{CR} from 83.9 to 174 ml/min is predicted to lead to an increase in total β-lactam clearance of 79.5% and a pronounced decrease in β-lactam concentrations. This may prove helpful for clinicians making decisions about β-lactam dosing regimens, especially to establish efficient initial dosing strategies and in situations when TDM is not available. The association between renal function and piperacillin concentrations and the consequence on target attainment is further demonstrated in Fig. 4. The maximum MIC resulting in a 90% PTA (100% fT_{MIC}) for a patient with a CL_{CR} of greater than 130 ml/min (by definition, ARC) is predicted to be 0.125 mg/liter, whereas it is predicted to be 4 mg/liter for a patient with a CL_{CR} of less than 60 ml/min. For the predefined PK/PD target of a 50% fT_{MIC}, the difference is even bigger, with a maximum MIC of 3 mg/liter for a CL_{CR} of greater than 130 ml/min and a maximum MIC of 32 mg/liter for a CL_{CR} of less than 60 ml/min. These findings imply that patients with renal impairment are more likely to achieve therapeutic piperacillin concentrations than patients with ARC. This is in line with the fact that patients with renal impairment are recommended lower piperacillin doses than patients with preserved renal function (10, 25). In Denmark, patients with a CL_{CR} of $<$30 ml/min are recommended reduced piperacillin-tazobactam doses, namely, IA at 4 g every 12 h (q12h). Although ARC is correlated with lower antibiotic concentrations, it has not yet been associated with clinical failure (16, 26).

As illustrated in our simulations and predictions, prolonged antibiotic infusion reduces the risk of subtherapeutic concentrations (Tables 3 and 4; Fig. 3). This is in line with the findings of other studies reporting similar findings following EI and CI, namely, an increased fT_{MIC} and a higher probability of target attainment (5, 14, 27–29). In our simulations, a 4-g loading dose preceded the infusion in the CI regimen, and the total daily dose was thus higher than that achieved with the IA and EI regimens. The loading dose would primarily bias the PTA calculation in the early phase of the infusion (the approach to steady state), but judging from the EI time course, the impact is assumed to be low. In addition to the PK/PD advantages reported, CI has also been suggested to reduce the daily antibiotic dose needed, which means lower costs for the hospitals (30). However, data on the clinical advantages of CI are controversial, and several reviews comparing clinical improvement and mortality rates are irresolute regarding the superiority of prolonged infusion over IA (30–34). Two large multicenter randomized controlled trials comparing clinical outcomes between β-lactam CI and IA in severe sepsis patients have recently been published. Dulhunty et al. (35) enrolled 432 patients

from 25 ICUs, including patients on renal replacement therapy. They found no difference in clinical outcome between the two patient groups. Abdul-Aziz et al. (36) included 140 patients from two ICUs and found opposite results; clinical cure rates were significantly higher in severe sepsis patients receiving a β-lactam by CI than those receiving a β-lactam by IA. As opposed to Dulhunty et al. (35), Abdul-Aziz et al. (36) did not include patients on renal replacement therapy. This may partially explain the difference in clinical cure rates between the two studies. Renal impairment, which is a common complication in critically ill patients, leads to a prolonged half-life for renally cleared antimicrobials. This results in a longer T_{MIC} and increases the probability of achieving therapeutic concentrations, regardless of the mode of administration of the drug (30). Thus, patients with renal impairment may not need prolonged antibiotic infusion to be clinically cured. It has been suggested that specific populations among the critically ill may benefit from prolonged infusion. Results from a post hoc analysis of data from the DALI study (3) found no overall difference in clinical outcome between patients receiving CI and patients receiving IA. However, in the subgroup analysis, there was a significant difference for patients with respiratory infections, with 30-day survival being higher for patients treated with CI than those treated with IA (37). Further research to identify such subpopulations that may benefit from prolonged infusion is needed. Moreover, the clinical benefits from continuous infusion are more pronounced when the infection is caused by a pathogen with reduced antibiotic susceptibility (38, 39).

In addition to prolonged infusion, our results demonstrate that a higher intermittent piperacillin dose of 16 g/day (IA at 4 g q6h) also increases the chance of PK/PD target achievement (Tables 3 and 4; Fig. 3). For piperacillin given by IA at 4 g q8h, the maximum MIC for a pathogen resulting in a 100% fT_{MIC} was 0.5 mg/liter (Table 4). With the increasing antimicrobial resistance seen worldwide, the number of pathogens with an MIC above 0.50 mg/liter is likely to increase, which indicates that empirical treatment with piperacillin at 4 g q8h may be insufficient. For piperacillin given by IA at 4 g q6h, the maximum MIC for a pathogen resulting in a 100% fT_{MIC} was 2.0 mg/liter (Table 4). This dosing regimen is already standard practice for treating septic patients in many countries (3, 14), and our results speak in favor of implementing such a dosing regimen in Denmark as well.

To assess the predefined PK/PD targets, we used the clinical breakpoint MIC for *P. aeruginosa* (16 mg/liter). Although the MIC of pathogens causing infections in septic patients is often lower than 16 mg/liter, a worst-case scenario like this needs to be considered because of the increasing rates of antimicrobial resistance seen globally and the increasing traveling patterns of patients today, which make physicians unaware of the pattern of susceptibility that they may be facing.

In conclusion, our results show that piperacillin administered as an intermittent bolus dose of 4 g q8h may result in subtherapeutic concentrations in septic patients. The impact of eCL_{CR} on piperacillin concentrations was quantified, and patients with augmented renal clearance have a reduced likelihood of achieving recommended PK/PD targets. To make sure that the least susceptible pathogens are targeted, prolonged infusion or dose increment needs to be considered in this patient population.

MATERIALS AND METHODS

Study design. The study was conducted as a prospective, observational study at the Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark, between November 2015 and June 2016 (ClinicalTrials.gov registration no. NCT02569086). The study was approved by the Danish Data Protection Agency. Given that this study was undertaken in parallel with standard-of-care treatment of suspected sepsis, the Regional Ethical Committee approved the study without requiring signed informed consent.

Patient population. Patients fulfilling the criteria for sepsis and treated empirically with piperacillin-tazobactam (Tazocin) at 4 g/0.5 g every 8 h were eligible for the study. Sepsis was defined according to the sepsis definitions from 2001 (40); thus, all patients fulfilled the systemic inflammatory response syndrome (SIRS) criteria and had a known or suspected infection. The assessment of a potential infection was made by the treating physician and was based on clinical signs and symptoms of infection and laboratory test results (i.e., elevated C-reactive protein levels and white blood cell counts). Patients were included within 48 h after initiation of treatment. Patients on renal replacement therapy and patients

under the age of 18 years were excluded. The following demographic and clinical data were registered for each enrolled patient: age, gender, body weight, plasma creatinine and plasma albumin levels, and estimated creatinine clearance (eCL_{CR}), derived from the Cockcroft-Gault formula (41).

Study drug and blood sample collection. Piperacillin-tazobactam (4 g/0.5 g) was administered intravenously (i.v.) as a 3-min bolus infusion. Serial blood samples were collected over one dosing interval for up to three consecutive days if piperacillin-tazobactam treatment was maintained. The sampling times were optimized in the PopED (version 2.13) optimal design tool (42), given a prior piperacillin PK model for septic shock patients (4), and were focused on providing information on the population PK and the individual fT_{MIC} (for further details, see A. N. Kristoffersson's unpublished presentation at the Population Optimum Design of Experiments [PODE] workshop, Uppsala, Sweden, 20 June 2016 [http://www.maths.qmul.ac.uk/~bb/PODE/PODE2016_AKristoffersson.pdf]). At the first day after study inclusion, each patient had three blood samples drawn. Patients 1 to 11 (group A) had blood samples drawn at 10 to 20 min, 45 to 75 min, and 7 to 8 h after administration of the drug. Patients 12 to 22 (group B) had blood samples drawn at 10 to 20 min, 2 to 3 h, and 7 to 8 h after administration of the drug. On days 2 and 3, patients in group A had blood samples drawn at 2 to 3 h and 7 to 8 h after administration of the drug and patients in group B had blood samples drawn at 45 to 75 min and 7 to 8 h after administration of the drug. For all enrolled patients, the exact time for blood sample collection was registered, and the entire dosing history of piperacillin was available for incorporation into the analysis data set.

Piperacillin was administered in combination with the β-lactamase inhibitor tazobactam. However, we determined only the piperacillin concentrations. Therefore, here we solely describe and discuss piperacillin dosing.

UHPLC analysis. The free concentrations of piperacillin in serum were assessed using ultra-high-performance liquid chromatography (UHPLC; Agilent 1290; Agilent Technologies, USA). Before UHPLC analysis, 300 μl of serum was placed in a 96-well ultrafilter plate with a 30-kDa-molecular-mass cutoff (Acroprep 30K Omega; Pall Corporation, USA). After centrifugation for 30 min at 1,000 $\times$ *g*, 15 μl filtrate was mixed with 20 μl of 10 mM phosphate buffer, pH 3 (NaH_2PO_4; H_2O was adjusted with HCl; Merck, Germany). For analysis, 5 μl was injected into the UHPLC system, which was equipped with a C_{18} column (particle size, 1.7 μm; 100 mm by 2.1 mm; Kinetex; Phenomenex, USA) that had been preheated to 40°C. Piperacillin was isolated with a gradient of acetonitrile (Sigma-Aldrich, Denmark) in phosphate buffer, changing from 20% to 30% over 2.5 min. Piperacillin was eluted with a typical retention time of 2.2 min and was measured with UV detection at 210 nm. Calculation of the concentrations was based on the piperacillin peak areas and was done with ChemStation software (Agilent Technologies, USA). Intrarun (total) imprecisions (coefficients of variation [CV]) were 10.2% (15.3%) at 4.5 mg/liter and 4.7% (8.2%) at 15.6 mg/liter. The limit of quantification was defined as the lowest concentration with a CV of $<$20% and was found to be 0.5 mg/liter.

PK/PD targets. The following PK/PD targets were evaluated: a 50% fT_{MIC} (in which the free piperacillin concentration was maintained above the MIC for at least 50% of the dosing interval) and 100% fT_{MIC} (in which the free piperacillin concentration was maintained above the MIC throughout the dosing interval). To evaluate the predefined PK/PD targets mentioned above, the piperacillin clinical breakpoint MIC for *Pseudomonas aeruginosa* (16 mg/liter) published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) was used (43). This represents a worst-case scenario regarding bacterial susceptibility, which is what empirical treatment is based upon.

Pharmacokinetic modeling. A population PK model was developed using NONMEM (version 7.3) software (Icon Development Solutions, Hanover, MD, USA) (44) and the programs Perl-Speaks-NONMEM and Piraña to assist with the execution of models and the overview (45). The first-order conditional estimation method with interaction was used to estimate model parameters. Model selection and evaluation were based on the goodness of fit and visual predictive checks (VPC) (46). For statistical assessment, the objective function values (OFV) of two nested models were compared using a likelihood ratio test under the assumption that the OFV is χ^2 distributed (a ΔOFV of 3.84 would be significant at a *P* value of 0.05 for one additional parameter).

For incorporation of patient covariates, a linear relationship $[1 + \theta_i \cdot (X_i - X_{median})$, where θ_i is the estimated covariate effect, X_i is the individual covariate value, and X_{median} is the median covariate value in the population] was used for continuous covariates, whereas a shift in the typical value for the least common category was used for categorical covariates. It was decided to carry continuous covariates backwards to previous occasions, without interpolation between measurements.

The model was developed to describe the collected plasma observations by initially testing one-, two-, or three-compartment disposition models in combination with linear elimination. Thereafter, the optimal description of interindividual variability (IIV) was sought by including variances on parameters when significant, assuming that these followed a log-normal distribution in the population.

After establishing an acceptable description of the data, patient covariates were tested to explain part of the random parameter variability. The primary focus was assessing eCL_{CR} on the elimination parameter, since piperacillin is primarily renally eliminated. Furthermore, weight was tested on PK parameters, in line with the allometric principle; i.e., an underlying PK process scales with weight through a power relationship, with exponents of 0.75 being used for clearance processes and 1.0 being used for distribution volumes.

Simulations. Based on the final model, predictions of the unbound piperacillin concentration-time course over 24 h were done following intermittent administration (IA), extended infusion (EI), and continuous infusion (CI). The predictions were performed for three piperacillin daily doses: 16 g, 12 g, and 8 g. The IA dosing regimens were 4 g every 6 h (q6h), 4 g every 8 h (q8h), and 4 g every 12 h (q12h),

administered as a short infusion over 3 min. The EI dosing regimens were 4 g q6h (infusion over 3 h), 4 g q8h (infusion over 4 h), and 4 g q12h (infusion over 6 h). The CI dosing regimens were 20 g/day, 16 g/day, and 12 g/day, including a loading bolus dose of 4 g, which is standard clinical practice when CI is initiated. The effect of eCL_{CR} on these profiles was demonstrated by showing predictions for eCL_{CR} equal to the population median and eCL_{CR} equal to the highest value observed in the current patient population. Furthermore, the individual patient parameter estimates (empirical Bayes' estimates) were used to predict the number of patients in the current population that would achieve the predefined PK/PD targets (50% and 100% fT_{MIC}) under the nine different treatment regimens described above. Lastly, the impact of random variability on a parameter with an identified covariate effect (e.g., the impact of eCL_{CR} on clearance) was examined to identify the degree of overlap for different covariate values.

Calculation of the probability of target attainment (PTA) for pathogen MICs ranging from 0.125 mg/liter to 128 mg/liter was done on the basis of 10,000 simulated data sets (i.e., 2,200,000 simulated patients).

PTA calculations for the nine dosing regimens were made for both predefined PK/PD targets. For a covariate included in the final population PK model, the individual values for that covariate were sampled from a distribution, instead of relying on the baseline point values measured in the studied patients.

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