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Neurotoxic Concentration of Piperacillin during Continuous Infusion in Critically Ill Patients

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ABSTRACT This retrospective cohort study included 53 patients admitted to the intensive care unit (ICU), with an average age of 69 years, without neurologic disorder before initiation of a continuous piperacillin infusion at the standard dose and who underwent piperacillin serum concentration monitoring. Among them, 23 developed a neurologic disorder for which the piperacillin causality was chronologically and semiologically suggestive. A concentration threshold of 157.2 mg/liter independently predicted neurotoxicity with 96.7% specificity and 52.2% sensitivity and may constitute a limitation when targeting less susceptible pathogens.

KEYWORDS β-lactams, intensive care unit, neurotoxicity, sepsis, therapeutic drug monitoring, β-lactams

Piperacillin is a β-lactam antibiotic, allowing bactericidal activity both against Gram-negative and Gram-positive bacteria. In combination with tazobactam as a β-lactamase inhibitor, it is among the most used broad-spectrum antibiotics in intensive care units (ICU) (1). Due to the variability of the pharmacokinetics (PK) in critically ill patients, therapeutic drug monitoring (TDM) of piperacillin is recommended in the ICU to adjust the dose according to the serum concentration (2). The pharmacokinetic-pharmacodynamic (PK/PD) relationship of β-lactams has been extensively studied to improve efficacy optimization, and the dose is adjusted according to the time the free (or unbound) drug concentration remains above the MIC of the infecting pathogen ($fT > $ MIC) (2). Moreover, administration of piperacillin by continuous infusion leads to higher median concentrations than standard bolus dosing and thus allows a higher probability of attainment of the 100% $fT > 4\times$ MIC minimum PK/PD target, which would be required in critically ill patients (3–6). Conversely, the upper value above which serum concentrations are not required is usually set at 100% $fT = 10\times$ MIC for dose reduction (2), but the toxic concentration threshold, especially when using continuous infusion, is unknown. Piperacillin like other β-lactams can be neurotoxic if excessively accumulated (7). The aim of our study was thus to determine the serum concentration of piperacillin administered by continuous infusion that would predict neurotoxicity in critically ill patients and thus improve the development of a rational strategy for dose adjustment based on routine TDM.

This retrospective cohort study was conducted at the medical ICU of the University Hospital of Amiens, Amiens, France. The patients included consisted of adults who received continuous intravenous (i.v.) infusion of piperacillin-tazobactam at the standard dose adjusted to the glomerular filtration rate (GFR) estimated by the modification of diet in renal disease (MDRD) formula (12 or 16 g/24 h for an estimated GFR [eGFR]

of $\geq$40 ml/liter/min/1.73 m², 12 g/24 h for an eGFR of $\geq$20 ml/min/1.73 m², and 8 g/24 h for an eGFR of <20 ml/min/1.73 m²) and who underwent monitoring of the piperacillin serum concentration over a 22-month period. The total serum concentration of piperacillin was measured after at least 48 h of treatment by a validated method combining high-performance liquid chromatography with photodiode array detection. For each patient, at least two investigators retrospectively reviewed the neurological evaluations daily recorded by the intensivists using the medical software of the ICU (Centricity Critical Care-Anandic Medical Systems AG, Switzerland). The basic neurological evaluation consisted of examination of the patient's mental status, cranial nerves, motor and sensory functions, coordination, and reflexes. For sedated patients, daily sedation interruption or alleviation allows assessment of neurologic function and detection of potential neurologic morbidity, as this has been proposed to shorten the length of stay in ICU (8). Patients who were showing any neurological disorder (ND) before the initiation of piperacillin and patients who did not undergo serum piperacillin measurement within the 24 h before or after the onset of an ND during piperacillin treatment were excluded. Patients who were pharmacologically sedated at the initiation of piperacillin or who had been sedated during piperacillin treatment were included if they were not showing any ND before the sedation induction. For included patients, the causality of piperacillin for an ND was considered suggestive when the 3 following criteria were met: (i) the ND presented as a symptom/sign consistent with piperacillin neurotoxicity (confusion, depressed level of consciousness, hallucinations, myoclonia, seizures according to the Common Terminology Criteria for Adverse Events of the National Institutes of Health, and awakening delayed by more than 24 h after stopping sedation), (ii) the ND occurred at least 48 h after the initiation of piperacillin, and (iii) the ND resolved or improved within 2 days after piperacillin discontinuation or dose reduction without starting renal replacement therapy. For each patient included, demographic data, medical history, and the simplified acute physiology score (SAPS II) at admission were collected. On the day of the piperacillin serum concentration measurement, we also examined the dose of piperacillin per 24 h the patient was receiving and whether the patient was febrile (body temperature more than 38°C), was septic according to standard criteria (9), and was also receiving or had also received up to 24 h previously renal replacement therapy, mechanical ventilation, vasopressive drugs, or potentially neurotoxic comedication (other β-lactams, fluoroquinolones, drugs of the central nervous system, drugs with atropine-like effects, and curare-like drugs). We also extracted biological data that are of interest for neurological evaluation. When a patient underwent several serum piperacillin measurements and did not show an ND during the treatment, the day of the highest measured concentration was selected for statistical analysis, so that each patient was included only once. The characteristics of the patients who developed an ND for which piperacillin causality was suggestive (piperacillin neurotoxicity group) were compared to those of the patients who did not develop an ND or who developed an ND for which piperacillin causality was not suggestive (the rest of the cohort). Categorical variables were analyzed using a chi-square or Fisher's exact test, and continuous variables were analyzed using Student's t test or a Mann-Whitney U test for parametric or nonparametric variables, respectively. A receiver operating characteristic (ROC) analysis was performed to determine the serum concentration value of piperacillin that predicts piperacillin neurotoxicity. A multivariate analysis of usual risk factors for neurotoxicity in the ICU was performed using a backward stepwise method for multivariable logistic regression models. All variables with a P value of <0.1 in the univariate analysis were included in the final regression model. All tests were two tailed, and a P value of <0.05 was considered to be statistically significant. Statistical analyses were performed using IBM SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA).

During the study period, 214 patients were treated with piperacillin-tazobactam. Among them, 129 (60.3%) underwent at least one piperacillin serum measurement, and 53 (24.8%) have been included for analysis according to previously described criteria. The clinical and biological data collected for included patients are detailed in Table 1.

TABLE 1 Comparison between patients who developed neurotoxicity for which piperacillin causality was suggestive and patients who did not show piperacillin neurotoxicity[a]

Parameter[b]	Result for[c]: Piperacillin neurotoxicity group (n = 23)	Rest of cohort (n = 30)	P value[d]
Demographic data and medical history at admission			
Women, %	39.1	23.3	0.2423
Age, median yr	65 (61.5–71.5)	71.5 (64.3–79.5)	0.0502
Wt, median kg	87 (68–99)	87.5 (78.3–99)	0.1778
BMI, median kg/m^2	29.6 (23.3–32.8)	28.4 (25–32.7)	0.6416
History of brain injury (stroke or trauma), %	13.0	0	0.0760
History of epilepsy, %	8.7	3.3	0.5730
History of alcoholism, %	17.4	13.3	0.7150
History of drug abuse, %	0	0	
History of cardiovascular disease, %	82.6	76.7	0.7379
History of cancer, %	43.4	60	0.2756
SAPS II, median	58 (46–76)	54 (42–73)	0.4454
Clinical data from day of piperacillin serum measurement			
Fever, %	30.4	20	0.5220
Sepsis, %	65.2	26.7	0.0006*
Mechanical ventilation, %	60.9	53.3	0.7800
Renal replacement therapy, %	26.1	26.7	1
Vasopressive comedications, %	82.6	46.7	0.0100*
Potentially neurotoxic comedications, %	73.9	80	0.7430
Hepatic impairment, %	30.4	13.3	0.1770
Biological data from day of piperacillin serum measurement			
Creatininemia, median μM	261 (170–349.5)	122 (54–242)	0.0169*
eGFR, median ml/min/1.73 m^2	18 (15–37)	50 (12–83)	0.0142*
Proteinemia, median g/liter	55 (51–60)	55 (42–64)	0.7060
Natremia, median mM	139 (137–144)	138 (130–141)	0.3726
Calcemia, median mM	1.9 (1.8–2)	2 (1.8–2.2)	0.1368
Lactatemia, median mM	1.6 (1.1–2.4)	1.5 (1.1–1.9)	0.3528
CRP, median mg/liter	149.6 (103–281.2)	144.3 (89.9–190.1)	0.1537
PCT, median μg/liter	25 (1.9–35.6)	2.48 (2.5–9.45)	0.0072*
pH, median	7.39 (7.35–7.47)	7.44 (7.39–7.47)	0.3173
Piperacillin treatment at initiation time			
Dose, median g/24 h	12 (12–12)	12 (12–12)	0.4866
Dose normalized to eGFR, median g/24 h/100 ml/min/1.73 m^2	36.4 (16–58.6)	28.6 (12.8–52.5)	0.5634
Piperacillin treatment on day of piperacillin serum measurement			
Dose, median g/24 h	12 (8–12)	12 (9–12)	0.9207
Dose normalized to eGFR, median g/24 h/100 ml/min/1.73 m^2	48 (35.3–69.7)	22 (14.3–54)	0.0111*
Serum concn, median mg/liter	156.9 (95.4–236)	91.3 (68.6–126.8)	0.0016*
Time from treatment initiation, median days	3 (2–5)	3 (2–5)	0.7819
fC/MIC, median	9.72 (5.35–15.06)	5.4 (3.6–7.9)	0.0174*

[a]Patients who developed neurotoxicity for which the piperacillin causality was suggestive are represented by the piperacillin neurotoxicity group, and those who did not show piperacillin neurotoxicity are indicated as the rest of the cohort.
[b]Abbreviations: BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; fC/MIC, free concentration of piperacillin over the MIC of the infective pathogen; PCT, procalcitonin; SAPS II, simplified acute physiology score.
[c]Interquartile ranges are shown in parentheses.
[d]*, significant at $P < 0.05$.

Reported NDs for which the piperacillin causality was considered suggestive were depressed level of consciousness in 11 patients (47.8%), delayed awakening after stopping sedation in 10 patients (43.5%), confusion in 5 patients (21.7%), myoclonia in 3 patients (13%), seizures in 1 patient (4.3%), and hallucinations in 1 patient (4.3%). Patients in the piperacillin neurotoxicity group were more septic (65.2 versus 26.7%; $P = 0.0006$), on vasopressive drugs (82.6 versus 46.7%; $P = 0.01$), and showed a lower eGFR (18 versus 50 ml/min/1.73 m^2; $P = 0.0142$) than patients in the rest of cohort. The median piperacillin dose normalized to eGFR was higher in the piperacillin neurotoxicity group than in the rest of the cohort (48 versus 22 g/24 h per 100 ml/min/1.73 m^2; $P = 0.0111$), while it was not different at the piperacillin initiation time (36.4 versus 28.6
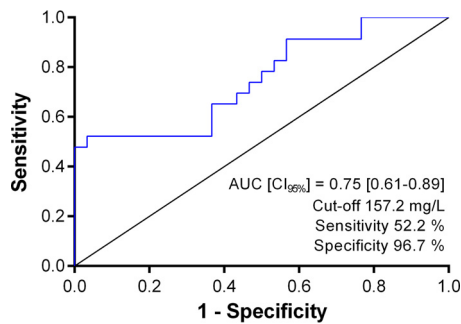
FIG 1 Receiver operating characteristic (ROC) curve of piperacillin serum concentration for predicting neurotoxicity.

g/24 h per 100 ml/min/1.73 m²; $P = 0.5634$). Indeed, the median dose and the median eGFR at the start of the treatment were not statistically different in patients who subsequently developed a suggestive piperacillin neurotoxicity compared to those who did not (dose of 12 versus 12 g/24 h, $P = 0.4779$, and eGFR of 33 versus 44 ml/min/1.73 m², $P = 0.3792$, respectively). Excluding patients who were on renal replacement therapy, we observed that the median percentage of decrease of eGFR between piperacillin initiation and piperacillin concentration measurements (on average 3 days) was significantly higher in patients with sepsis (-35.6% versus -6.1%, respectively; $n = 39$, $P = 0.0269$). Then we found that the piperacillin serum concentration was significantly higher in the piperacillin neurotoxicity group than in the rest of the cohort (159.9 versus 91.3 mg/ml; $P = 0.0016$). It could thus be hypothesized that the dose has not been always adjusted adequately to the sepsis-associated GFR changes and that the first piperacillin serum measurement was generally too late to anticipate the rapid piperacillin accumulation. Based on the concentration data from the overall cohort, ROC analysis found a predictive serum concentration threshold for the occurrence of piperacillin neurotoxicity of 157.2 mg/liter with 96.7% specificity and 52.2% sensitivity (area under the concentration-time curve [AUC], 0.75; 95% confidence interval [CI], 0.61 to 0.89) (Fig. 1). The high specificity of this threshold suggests that piperacillin neurotoxicity would be almost systematic at a higher concentration. This was corroborated by multivariable analysis showing that a piperacillin concentration equal or higher than 157.2 mg/liter was an independent risk factor of piperacillin neurotoxicity with an odds ratio of 14.86 (95% CI, 1.27 to 173.23; $P = 0.0313$) (Table 2). Conversely, none of the other factors, including sepsis, were found as independent risk factors. Although sepsis is a well-known cause of encephalopathy in ICUs (10), our results suggest that sepsis may constitute an indirect cause of NDs, promoting drug neurotoxicity at least by inducing GFR decrease and then drug accumulation. However, the 157.2-mg/liter concentration threshold also exhibits moderate sensitivity, indicating that piperacillin neurotoxicity would still occur at a lower concentration. The neurotoxic piperacillin concentration threshold is thus likely to be lower in patients that have accumulated several neurological risk factors, especially causes of blood-brain barrier permeability increase.

Nevertheless, the neurotoxic threshold of the piperacillin serum concentration shouldn't be interpreted without considering PK/PD targets for dose adaptation. The clinical benefits of the continuous infusion strategy are supported by the results of recent meta-analyses, especially for patients with a high sickness severity and infected by less-susceptible pathogens, such as nonfermenting Gram-negative bacilli (11–13). In our cohort, the infective organism was not identified for 19 of the 53 patients (35.8%). It was an *Enterobacteriaceae* family member in 17 patients (32.1%), *Pseudomonas aeruginosa* in 10 patients (18.9%), *Staphylococcus aureus* in 3 patients (5.7%), and another organism in 4 patients (7.5%). Considering 30% serum protein binding and EUCAST's epidemiological MIC cutoff values for identified organisms or the MIC of 16 mg/liter for nonidentified organisms, the median free piperacillin serum concentration

TABLE 2 Logistic regression analysis of risk factors for piperacillin neurotoxicity in critically ill patients

Risk factor of neurotoxicity	Odds ratio (95% CI)	P value
Univariate analysis		
Women	2.11 (0.64–6.94)	0.2183
Age of >68 yr	0.49 (0.16–1.48)	0.2082
History of brain injury (stroke or trauma)	ND[a]	
History of epilepsy	2.76 (0.23–32.5)	0.4193
History of alcoholism	1.37 (0.3–6.18)	0.6833
Fever of >38°C	1.75 (0.5–6.17)	0.3843
Sepsis	5.16 (1.59–16.77)	0.0064
Invasive mechanical ventilation	1.36 (0.45–4.1)	0.5837
Renal replacement therapy	0.97 (0.28–3.33)	0.9622
Vasopressive comedication	5.43 (1.49–19.82)	0.0105
Potentially neurotoxic comedication	0.70 (0.19–2.57)	0.6006
Hepatic impairment	2.84 (0.72–11.27)	0.1369
eGFR of <30 ml/min/1.73 m²	2.81 (0.91–8.68)	0.0721
Natremia of <135 mM	1.37 (0.30–6.17)	0.6833
Calcemia of <2 mM	2.61 (0.83–8.18)	0.0993
Lactatemia of >5 mM	ND	
pH of <7.35	3.18 (0.7–14.42)	0.1343
Piperacillin concn of ≥157.2 mg/liter	26.58 (3.08–229.32)	0.0028
Multivariate analysis		
eGFR of <30 ml/min/1.73 m²	1.37 (0.31–5.97)	0.6769
Vasopressive comedications	1.78 (0.37–8.54)	0.4705
Sepsis	2.36 (0.52–10.66)	0.2656
Calcemia of <2 mM	3.55 (0.78–16.18)	0.1013
Piperacillin concn of ≥157.2 mg/liter	14.86 (1.27–173.23)	0.0313

[a]ND, not determinable.

over MIC ratio was significantly higher in the piperacillin neurotoxicity group than in the rest of the cohort (9.7 versus 5.4, respectively, $P = 0.0174$). Importantly, the 100% $fT = 10\times$ MIC published threshold for dose reduction would allow neurotoxic piperacillin concentrations in cases of MICs from 12 mg/liter. A 16-mg/ml susceptibility breakpoint for piperacillin-tazobactam against *Pseudomonas aeruginosa* may thus incite clinicians to maintain a potentially neurotoxic dosage of piperacillin since the therapeutic window for 100% $fT = 4\times$ MIC to $fT = 10\times$ MIC would set the total serum concentration target between 83.2 and 208 mg/liter.

The primary limitations of this study are the retrospective design and the small cohort. Larger prospective and multicenter clinical studies including standardization of the neurological evaluation of ICU patients are needed to define more accurately the neurotoxic concentration threshold of piperacillin and risk factors. Moreover, the value we found here applies only to continuous infusion, and thresholds should be specifically defined for intermittent and extended infusions. Another important limitation is the use of MDRD in daily estimation of GFR for dose adjustment and for describing renal dysfunction. Creatinine-based GFR estimates rely on stable serum creatinine concentrations which cannot be present in the ICU. Nevertheless, MDRD may still be relevant in the ICU to predict clearance changes and PK/PD target attainment, as described for ceftazidime (14, 15).

Finally, this study is the first interested in the concentration-neurotoxicity relationship of piperacillin administered combined with tazobactam through continuous infusion in critically ill patients. A piperacillin serum concentration of 157.2 mg/liter would be predictive of neurotoxicity and constitute a concrete and useful criterion for the decision to reduce the piperacillin dose or, in case of a low-susceptibility pathogen, to switch to another antibiotic according to microbiological data and close TDM.

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