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ORIGINAL ARTICLE

Continuous infusion of ceftolozane/tazobactam is associated with a higher probability of target attainment in patients infected with *Pseudomonas aeruginosa*

Benoît Pilmis[1,2] · Grégoire Petitjean[3,2] · Philippe Lesprit[4] · Matthieu Lafaurie[5] · Najoua El Helali[3,6] · Alban Le Monnier[3,2,6] · on behalf the ATB PK/PD study group

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Abstract

Ceftolozane/tazobactam (CTZ/TZ) exhibits time-dependent antimicrobial activity, and prolonged infusion can better achieve the pharmacodynamic target than an intermittent bolus. We aimed to compare the use of prolonged or continuous infusion with intermittent administration of CTZ/TZ for the treatment of infections caused by multidrug-resistant *Pseudomonas aeruginosa*. We performed a multicentric prospective cohort study to evaluate continuous, prolonged, or intermittent infusion of CTZ/TZ. We assessed the plasma concentration as a function of the duration of infusion and then performed a simulation of the percentage of patients who would reach the PK/PD targets, set at 100% $fT_{> MIC}$ or 100% $fT_{>4\ MIC}$. Seventy-two patients were enrolled with a median [IQR] age of 48.5 [32.4–63.2] years. Fifty-seven (79%) were hospitalized in an intensive care unit. Thirty-seven (51.4%) were immunosuppressed, and the in-hospital mortality rate was 15.2%. The major site of infection was the respiratory tract (66.7%). The PK/PD objectives (100% $fT_{>4\ MIC}$) were achieved for all patients infected with strains with CTZ/TZ MICs < 4 mg/L, regardless of the mode of administration. In contrast, intermittent bolus administration and prolonged infusion did not achieve the PK/PD objectives when the CTZ/TZ MICs were ≥ 4 mg/L. However, the PK/PD objectives (100% $fT_{>4\ MIC}$) were achieved for strains with MICs up to 8 mg/L in patients receiving continuous infusion of CTZ/TZ. A dosing regimen of 2 g/1 g CTZ/TZ administered every 8 h as a 1-h intravenous infusion, as currently recommended, did not provided adequate coverage to achieve a sufficient probability of target attainment for *P. aeruginosa* strains with MICs ≥ 4 mg/L.

Keywords *Pseudomonas aeruginosa* · Ceftolozane/tazobactam · Pharmacokinetic/pharmacodynamic · Multidrug resistant

✉ Benoît Pilmis
bpilmis@hpsj.fr

[1] Equipe Mobile de Microbiologie Clinique, Groupe Hospitalier Paris Saint-Joseph, Paris, France

[2] EA4043 Unité Bactéries Pathogènes et Santés (UBaPS), Université Paris-Sud Saclay, Chatenay-Malabry, Orsay, France

[3] Plateforme de Dosage des Anti-infectieux, Groupe Hospitalier Paris Saint-Joseph, Paris, France

[4] Service de Biologie Clinique, Hôpital Foch, Suresnes, France

[5] Unité d'Intervention en Infectiologie (U2i), Hôpital Saint-Louis, Paris, France

[6] Laboratoire de Microbiologie Clinique, Groupe Hospitalier Paris Saint-Joseph, Paris, France

Abbreviations

AST	Antimicrobial susceptibility tests
CTZ/TZ	Ceftolozane/tazobactam
HRAM	High-resolution accurate mass
IQR	Interquartile range
MIC	Minimal inhibitory concentrations
PD	Pharmacodynamic
PK	Pharmacokinetic
UHPLC	Ultra-high performance liquid chromatography

Introduction

Ceftolozane/tazobactam (CTZ/TZ) is a combination of a novel cephalosporin and a beta-lactamase inhibitor with activity against Gram-negative bacilli, such as *Pseudomonas*

aeruginosa and *Enterobacteriaceae*, including multidrug-resistant strains [1]. During the last decade, the prevalence of infections caused by multidrug-resistant *P. aeruginosa* has increased [2]. The success of antibiotic therapy depends on the selection of empirical conditions that will assure a definitive cure, as well as the mode of administration [3, 4].

As the effect of antibiotics is time-dependent, the most important pharmacokinetic (PK)/pharmacodynamic (PD) parameter for CTZ/TZ activity is the duration of time over which the unbound (or free) drug concentration remains above the minimal inhibitory concentration (MIC) ($fT_{>MIC}$) [5]. Intermittent-bolus (IB) dosing, which is the most common mode of β-lactam administration, often results in suboptimal drug concentrations, especially in critically ill patients with conserved renal function [6, 7]. Many PK/PD simulation studies suggest that optimal β-lactam exposure is rapidly obtained via continuous infusion or extended 2- to 4-h infusion [6, 8].

We aimed to determine whether CTZ/TZ given every 8 h by intermittent administration, as currently recommended, results in therapeutic plasma concentrations in patients with multidrug-resistant *P. aeruginosa*-related infections.

Methods

We performed a prospective multicenter cohort study to compare prolonged or continuous infusion versus intermittent administration of CTZ/TZ for the treatment of multidrug-resistant *P. aeruginosa*-related infections. Multidrug resistance was defined, according to an international expert proposal by Magiorakos et al. [9], as non-susceptibility to at least one agent in three or more antimicrobial categories (extended-spectrum penicillins, carbapenems, cephalosporins, aminoglycosides, or fluoroquinolones).

All patients for whom data on the plasma concentrations of CTZ/TZ were available were eligible for this study. Plasma concentrations of CTZ/TZ at steady state were measured by UHPLC-ESI-HRAM (high-resolution accurate mass).

Antimicrobial susceptibility testing (AST) was performed using the disk-diffusion method according to the CA-SFM/EUCAST guidelines [10]. MICs of CTZ/TZ were determined by E-test strips in accordance with the manufacturer's recommendations.

We measured plasma concentrations at steady state according to the infusion duration of CTZ/TZ: ≤ 1 h (intermittent bolus group—IB), 4 h (prolonged infusion group—PI), and continuous infusion of the antibiotic (continuous infusion group—CI).

We then performed a simulation of the percentage of patients who would reach the PK/PD targets set at 100% $fT_{>MIC}$ or 100% $fT_{>4\ MIC}$ for the three groups of patients, depending on the MIC of CTZ/TZ against *Pseudomonas aeruginosa* and based on the results of the plasma assays performed on these patients. We chose targets considered to be the most appropriate for intensive care unit (ICU) patients treated with beta-lactams [7].

Results

Seventy-two patients were enrolled in the study. The median [IQR] age was 48.5 [32.4–63.2] years, and most patients were male (63.9%). The average (SD) weight was 70.5 (± 27.9) kg, and the measured clearance CL_{Cr} was 81.9 ± 52.3 mL/min (range 2 to 256 min). Patient characteristics are presented in Table 1.

Fifty-seven (79%) patients were hospitalized in ICUs. Thirty-seven (51.4%) were immunosuppressed, and the in-hospital mortality rate was 15.2%. The major sites of infection were the respiratory tract (66.7%), primary bacteraemia (7%), skin and soft tissue infections, and bones and joints infection (5.5% each).

No adverse events related to CTZ/TZ administration were reported during the study. CTZ/TZ MICs ranged from 0.5 to 8 mg/L. Nineteen (26.3%) patients were infected with strains with CTZ/TZ MICs ≥ 4 mg/L. The distribution of MIC is presented in Fig. 1.

Of the 72 patients enrolled in the study, 44 (61%) received IB, 13 (18%) PI, and 15 (21%) CI. The PK/PD objectives (100% $fT_{>4\ MIC}$) were achieved for all patients infected with strains with CTZ/TZ MICs < 4 mg/L, regardless of the mode

Table 1 Participant demographics and baseline characteristics

Clinical variable	Mean (SD)	Median [IQR]
Age (years)	45.4 (± 25.7)	48.5 [32.4–62.2]
Gender, (M/F)	(46/26)	–
Total body weight (kg)	70.5 (± 27.9)	67 [50.7–85]
Serum creatinine (μmol/L)	95.6 (± 67.6)	71 [58.2–122]
Measured glomerular filtration rate (mL/min)	81.9 (± 52.3)	68.5 [29.5–125]

SD standard deviation, *IQR* interquartile range

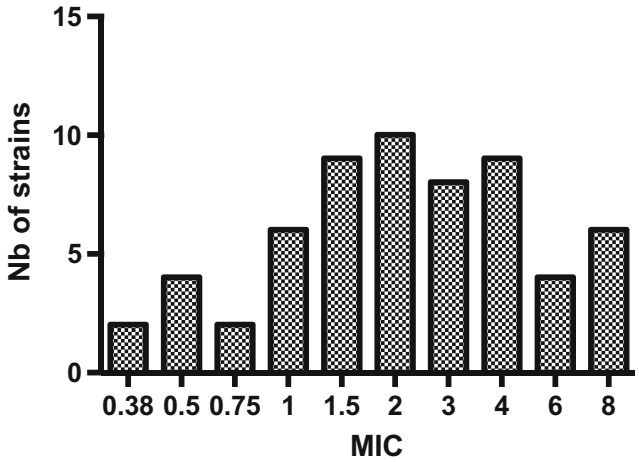

Fig. 1 CTZ/TZ MIC distribution of strains included in our study

of administration. In contrast, IB administration and PI did not achieved the PK/PD objectives when the CTZ/TZ MICs were ≥ 4 mg/L. However, the PK/PD objectives (100% $fT_{>4\ MIC}$) were achieved for strains with MICs up to 8 mg/L for patients receiving CI of CTZ/TZ.

We simulated the PK profiles at steady-state of intravenously administered CTZ/TZ (Fig. 2), clearly showing the differences according to the mode of administration (IB, PI, or CI). The duration of administration influenced the probability of target attainment (PTA) for the same dosing regimen, with higher PTA rates for patients treated by CI than those treated by IB administration or PI.

Discussion

This is the first study to evaluate the pharmacokinetics and pharmacodynamics of extended infusion of CTZ/TZ in patients treated for multidrug-resistant *P. aeruginosa*-related

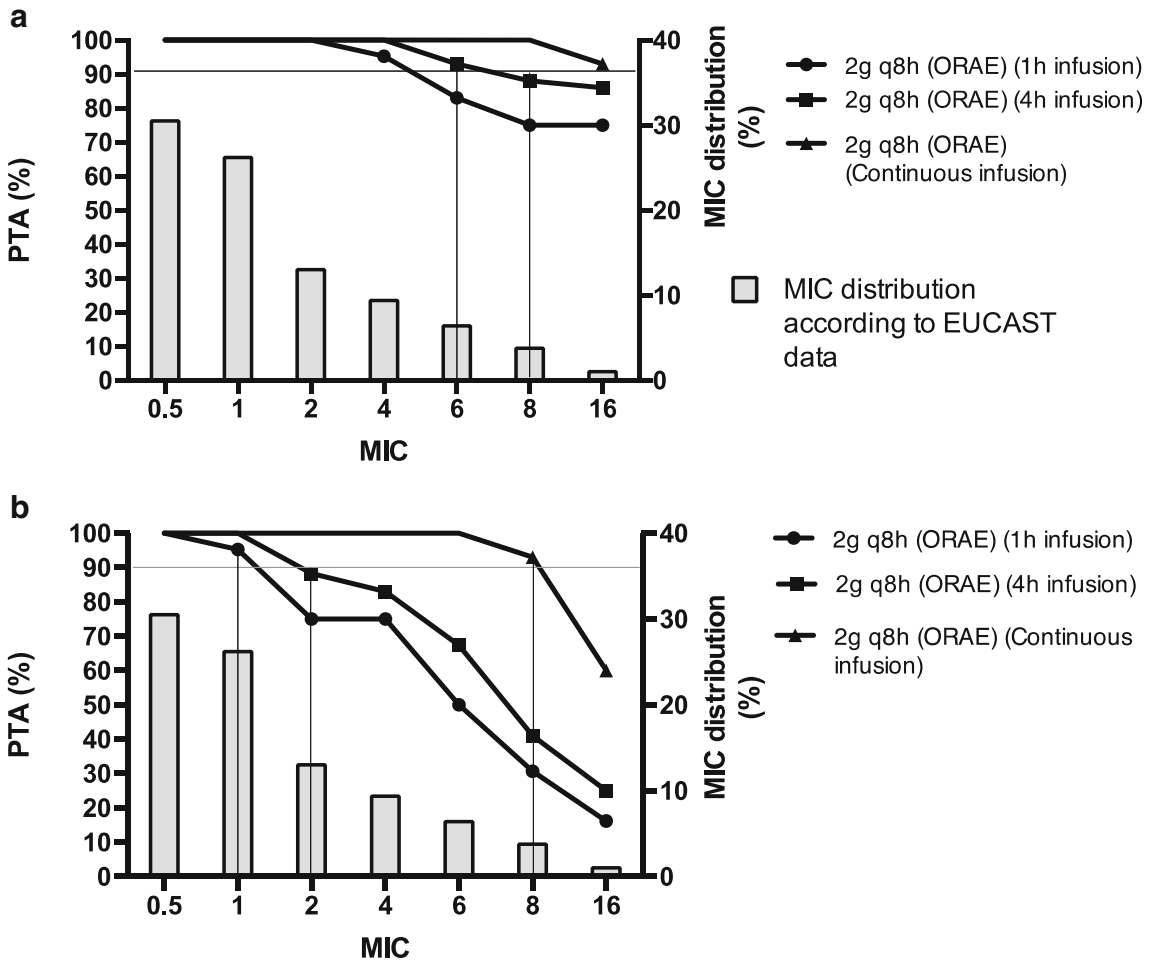

Fig. 2 PTA for CTZ at a $fT > MIC$ of 90% (**a**) and a $fT > 4 \times MIC$ of 90% (**b**) for intermittent bolus (1 h), prolonged infusion (4 h), and continuous infusion of CTZ/TZ at specific MICs in adults. The horizontal line represents a PTA of 90%. T_{Mic}, the cumulative percentage of the dosing interval that the drug concentration exceeds the MIC or 4 × MIC for the organism(s) under steady-state pharmacokinetic conditions; ORAE. or renally adjusted equally

infections. For a CTZ/TZ MIC of 6 mg/L, every regimen of 2 g *t.i.d.* or renally adjusted equivalent (ORAE) in our study achieved a PTA of > 90% $fT_{>MIC}$. However, only prolonged or continuous infusions achieved the objectives in more than 90% of cases if the MIC was ≥ 6 mg/L. Nevertheless, the time target above MIC ($fT_{> MIC}$) is relevant only for mild to moderate infections and seems inappropriate in the context of an ICU, where infections are more severe. Indeed, the objective is to achieve a concentration of 4- to 8-fold above the MIC for an equal amount of time for 100% of the interval between two administrations [11, 12].

Given these conditions and a CTZ/TZ MIC of 4 mg/L, only continuous infusions of 2 g *t.i.d.* ORAE achieved a PTA of > 90% patients with $fT_{>4\ MIC}$, whereas none of the regimens achieved optimal exposure if the MIC was > 16 mg/L.

These findings are in accordance with those of previous studies. A retrospective study by Lodise et al. of critically ill patients with *P. aeruginosa*-related infections found that extended infusions of piperacillin-tazobactam, to increase T > MIC, resulted in better 14-day survival (12.2% vs 31.6%, $p = 0.04$) of a subpopulation of severely ill patients (APACHE II score > 17) than that of a historical cohort [13]. Furthermore, findings from a hollow-fiber infection model study of a clinical *P. aeruginosa* isolate (CTZ/TZ MIC of 4 mg/L) suggest that higher doses of CTZ/TZ (2 g/1 g) are needed to prevent the emergence of antibiotic resistance in seriously ill patients with *Pseudomonas aeruginosa*-related infections [14].

Conclusion

A dosing regimen of 2 g/1 g CTZ/TZ administered every 8 h as a 1-h intravenous infusion, as currently recommended, did not provide adequate coverage to achieve a sufficient joint PTA for *P. aeruginosa* strains with MICs > 4 mg/L. Further studies are needed to better understand the optimal use of this new antibiotic regimen.

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PK/PD Study group
Aurelien Dinh, Marine de Laroche, François Parquin (Intensive Care Unit), Dominique Grenet (Pulmonary medicine), Eric Farfour (Clinical Biology), Antoine Roux (Pulmonary medicine), Sandra de Miranda (Pulmonary medicine), Gauthier Péan de Ponfilly (Clinical Biology), Matthieu Legrand (Serious Burn Unit), François Dépret (Serious Burn Unit), Mourad BENYAMINA (Serious Burn Unit).

Compliance with ethical standards

Conflict of interest BP: MSD: conference invitation, lecture fees
GP: None reported
PL: None reported
ML: None reported
NEH: None reported
ALM: MSD: conference invitation

Ethical approval Not applicable

Informed consent Not applicable

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