International Journal of Antimicrobial Agents 53 (2019) 520–524

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Short Communication

Clinical characteristics and prognosis of infections caused by *OXA-48* carbapenemase-producing Enterobacteriaceae in patients treated with ceftazidime-avibactam

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ARTICLE INFO

Article history:
Received 6 December 2017
Accepted 17 November 2018

Editor: Professor Matthew Falagas

Key words:
Carbapenemase
Enterobacteriaceae
Ceftazidima-avibactam
Treatment
Mortality
Adverse events

ABSTRACT

Background: Ceftazidime-avibactam has in vitro activity against Gram-negative bacilli that produce Class A, C and some D β-lactamases, and has been successfully used in the treatment of infections caused by cephalosporin and carbapenem-resistant Enterobacteriaceae. However, actual experience in the treatment of *OXA-48* carbapenemase-producing Enterobacteriaceae (CPE) is limited.

Objective: To review the characteristics and prognosis of *OXA-48* CPE infections treated with ceftazidime-avibactam since introduction of the drug to the current centre during the period October 2014 to December 2016.

Methods: Retrospective assessment of episodes of infection caused by *OXA-48* CPE treated with ceftazidime-avibactam, analysing data collected from infection diagnosis until 90 days after the end of treatment.

Results: Twenty-four episodes were analysed. Ceftazidime-avibactam was given as the initial definitive treatment in 15 (62.5%) and as salvage therapy in nine (37.5%). Intraabdominal (seven, 29%), urinary (six, 25%) and respiratory (five, 21%) were the most common sources. The 30-day and 90-day mortality rates were 8.3% and 20.8%, respectively. Clinical cure at 30 days was achieved in 62.5% of episodes. Four (16.7%) patients had adverse events, two of them were related to impaired renal function. Among patients who finished the treatment with ceftazidime-avibactam, seven (35%) were diagnosed with infection recurrence within 90 days of the end of treatment.

Conclusions: From experience, ceftazidime-avibactam is an effective drug for treating infections due to *OXA-48* CPE. From these results a better safety profile than the current best available therapy could be expected.

1. Introduction

Carbapenemase-producing Enterobacteriaceae (CPE) are an emerging global problem due to their ability to easily disseminate, and toxicity of the available therapy to date [1]. Ceftazidime-avibactam is a combination of ceftazidime with a new diazabicyclooctanone β-lactamase inhibitor, avibactam, which inhibits the activities of Ambler Class A and C β-lactamases and some Class D enzymes, including the KPC and *OXA-48* carbapenemases. Clinical trials performed on patients with complicated urinary tract infections and intraabdominal infections, including infections caused by cephalosporin-resistant Gram-negative isolates, have reported that ceftazidime-avibactam is effective and safe in these clinical settings [2-6]. However, few patients with infections caused by CPE were included. Some published observational studies have provided data on the efficacy of ceftazidime-avibactam for treating CPE infections [7,8]. Another recent study evaluated the efficacy of ceftazidime-avibactam as salvage therapy in patients with *OXA-48* CPE infection, with promising results [9]. However, experience in treating these infections remains scarce.

The aim of this study was to describe experience with the use of ceftazidime-avibactam in patients with *OXA-48* CPE infections in a 750-bed university hospital. Factors associated with mortality,

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https://doi.org/10.1016/j.ijantimicag.2018.11.015
0924-8579/

clinical failure, and adverse events related to the treatment were evaluated.

2. Methods

A retrospective study was conducted on patients with *OXA-48* CPE and *OXA-48*-like infections who had received treatment with ceftazidime-avibactam for at least 72 hours since introduction of the drug to the current centre during the period October 2014 to December 2016. Three of those were included in a previous study about the efficacy of ceftazidime-avibactam [7]. *OXA-48* CPE infection was defined by the isolation of the microorganism in a blood culture or in a clinical sample of a patient with significant symptoms and signs of infection at that location. Patients with any source of infection were included. Carbapenemase production was suspected when routine susceptibility testing showed reduced susceptibility to carbapenems, according to the clinical breakpoints and screening cut-off values for carbapenemase-producing Enterobacteriaceae proposed by EUCAST [10]. Confirmation of *OXA-48* and *OXA-48*-like production was achieved by testing the susceptibility to temocillin (> 32 mcg/mL) and using a rapid immunochromatographic test (*OXA-48* K-Set, CORIS BioConcept) and/or a real-time PCR (GeneXpert, Xpert Carba-R, Cepheid, Sunnyvale, CA, USA). Isolates were analysed by pulsed field gel electrophoresis using the enzyme XbaI (New England BioLabs, Beverly, MA, USA) [11]. Multilocus sequence typing was performed according to the method by Diancourt et al. with seven housekeeping genes: *rpoB, gapA, mdh, pgi, phoE, infB*, and *tonB* [12]. Antimicrobial susceptibility testing was performed by microdilution (Phoenix System, Becton-Dickinson, Sparks, MD, USA and Sensititre, Thermo Scientific, Trek Diagnostic Systems Ltd, West Sussex, UK), Etest (bioMérieux, SA, Mercy-l'Etoile, France) or disk diffusion methodologies.

Results were analysed using the EUCAST breakpoint tables to interpret MICs and zone diameters. A standard dosage of ceftazidime-avibactam (2 g of ceftazidime with 0.5 g of avibactam intravenously every 8 h as a 2-h infusion) was used, with adjustments in case of kidney failure following manufacturer recommendations. Ceftazidime-avibactam could have been used as the initial treatment or as salvage therapy if during the course of infection. The drug was prescribed based on compassionate use, so that all patients or their legal representatives provided written informed consent. Demographic variables, previous antibiotic treatment, data regarding severity of the infection, source, presence of bacteraemia, and empirical and definitive antibiotic treatment were recorded. Empirical therapy was considered appropriate should the patient have received at least one active drug in the first 48 h after sample collection and before any antibiotic susceptibility was reported.

In terms of definitions, clinical cure was defined as the survival, resolution of symptoms and signs of infection, and absence of recurrence within 30 days following the onset of treatment with ceftazidime-avibactam, with negative infection site cultures in those patients in whom control samples were obtained. Recurrence of infection was defined as the appearance of signs and symptoms of infection in the same or different location with positive cultures for *OXA-48* CPE within 90 days of the end of treatment with ceftazidime-avibactam. Thirty-day and 90-days mortality were recorded. Lastly, adverse events were defined as any untoward effect that started to manifest itself during the course of ceftazidime-avibactam treatment that could be attributed to the drug.

Statistical analysis was carried out using IBM SPSS statistics version 19. Continuous variables were expressed either as mean (standard deviation, SD) or median (interquartile range, IQR), and compared using the Student's *t*-test or Mann-Whitney test. Categorical variables were expressed as absolute frequency (%), and compared using the χ^2 test or Fisher's exact test when necessary. A *P* value < 0.05 was considered statistically significant.

Table 1
Clinical characteristics of the 23 patients (24 episodes) with *OXA-48* CPE infection.

Age, mean years (SD)	58.85 (16.03)
Male gender	19 (82.6)
Prior colonisation	6 (26.1)
Place of acquisition	
- Hospital ward	12 (50.0)
- ICU	8 (33.3)
- Other health-care related	4 (16.7)
Admission within the previous 3 months	14 (60.8)
Admission within the previous 6 months	15 (65.2)
Diabetes mellitus	7 (30.4)
Cardiovascular disease	8 (34.8)
Liver cirrhosis	3 (13.0)
Chronic renal failure	10 (43.5)
Chronic pulmonary disease	6 (26.1)
Solid organ/haematological cancer	5 (21.7)
HIV infection	1 (4.3)
Immunosuppressive treatment	5 (21.7)
Solid organ transplantation	5 (21.7)
Charlson Comorbidity Index, mean (DS)	4.3 (2.9)
McCabe prognosis of underlying disease	
- Non-fatal	12 (52.2)
- Ultimately fatal	11 (47.8)
Alcoholism	1 (4.3)
Days from hospital admission to infection, median (IQR)	19.5 (IQR 7.5-62)
SOFA score, mean (DS)	3.3 (2.8)

The denominator is the total number of patients (n = 23) for all characteristics except for Place of acquisition, Days from hospital admission to infection, Need for ICU admission and SOFA score, where the number of episodes (n = 24) were considered.
Abbreviations: SD, standard deviation; ICU, intensive care unit; HIV, human immunodeficiency virus; SOFA, sequential organ failure assessment; IQR, interquartile range; SST, skin-soft tissue.

3. Results

3.1. Patient characteristics and source of infection

Twenty-three patients, one of whom had two episodes of infection by CPE, who were treated with ceftazidime-avibactam were analysed. The mean age was 58.8 years (SD 16.0) and 19 patients (82.6%) were male. Patients' underlying comorbidities are shown in Table 1.

All patients had received antibiotic treatment within the 3 months prior to the infection, with carbapenems in 18 (75%) episodes and third-generation cephalosporins in eight (33.3%). The most common source of infection was intraabdominal (seven, 29.2%), followed by urinary tract infection (six, 25%), pneumonia (five, 20.8%; three were ventilator-associated), osteoarticular/skin-soft tissue infection (four, 16.7%), device-related meningitis (one), and catheter-related bacteraemia (one). Eight (33.3%) episodes presented with bacteraemia and four (16.7%) with septic shock.

3.2. Organisms and antimicrobial susceptibility

Klebsiella pneumoniae was present in 23 (95.8%) episodes and *Escherichia coli* in one. In addition to the *OXA-48* carbapenemase, all but one isolates produced ESBLs (CTX-M15 in all of them). All strains contained the sequence type ST101. If they were analysed by pulsed field electrophoresis, differences in the evolution were found throughout the study period, so for this reason it was not considered an outbreak.

Antimicrobial susceptibility of isolates is shown in Table 2. Based on EUCAST criteria, 45.8% of the tested isolates were susceptible to meropenem, 62.5% to imipenem, and 50% to tigecycline. Out of 17 tested isolates, one (5.9%) showed resistance to colistin.

Table 2
Antimicrobial susceptibility of isolates.

Antibiotic (number of isolates tested)	Susceptible	Intermediate	Resistant
Ceftazidime (24)	1 (4.2)		23 (95.8)
Amikacin (24)	19 (79.2)	3 (12.5)	2 (8.3)
Gentamicin (24)	17 (70.8)		7 (29.2)
Colistin (17)	16 (94.1)		1 (5.8)
Ertapenem (24)			24 (100.0)
Imipenem (24)	15 (62.5)	4 (16.7)	5 (20.8)
Meropenem (24)	11 (45.8)	7 (29.2)	6 (25.0)
Tigecycline (18)	9 (50.0)	6 (33.3)	3 (16.7)
Trimethoprim-sulfamethoxazole (24)	1 (4.2)		23 (95.8)
Ciprofloxacin (24)			24 (100.0)
Fosfomycin (11)	1 (9.1)		10 (90.9)

All the isolates were susceptible to ceftazidime-avibactam with MIC $\leq$ 1 mg/L.

All isolates were susceptible to ceftazidime-avibactam, with an MIC of 0.5 mg/L for 23 isolates and 1 mg/L for the remaining one.

3.3. Treatment

In 14 (58.3%) episodes, adequate empirical treatment was prescribed within 48 hours of sample collection. Once the diagnosis of CPE was made, ceftazidime-avibactam was the initial treatment choice in 15 (62.5%) episodes, with a mean of 2.5 days (SD 1.7) elapsing from sample collection to the beginning of this treatment. In nine (37.5%) episodes, ceftazidime-avibactam was prescribed during the course of infection, with a mean of 14.4 days (SD 12.2) between diagnosis of infection and prescription. Ceftazidime-avibactam was administered as monotherapy in 14 (58.3%) episodes and in combination regimens in 10 (41.7%), with amikacin (n = 1), colistin (n = 1), tigecycline (n = 3) or a combination of two of these drugs (n = 5).

Patients receiving combination treatment showed pneumonia more often than those receiving monotherapy (40% vs. 7.1%, $P = 0.12$), and showed a greater severity of the disease with a higher SOFA score (4.7, SD 2.8 vs. 2.4, SD 2.3, $P = 0.035$) and presence of severe sepsis or septic shock at diagnosis (40% vs. 14.3%, $P = 0.192$). The median duration of ceftazidime-avibactam treatment was 14 days (IQR 8.5–30).

3.4. Outcomes

The 30-day and 90-day mortality rates were 8.3% (2/24) and 20.8% (5/24), respectively. Death was related to uncontrolled infection in three patients: one with ventilator-associated pneumonia and two with intraabdominal abscesses (secondary to acute pancreatitis in one case and to cholangitis in the other). Thus, infection-related mortality at 30 days and 90 days was 8.3% and 12.5%, respectively. Patients who died within 90 days of infection diagnosis were generally older, and showed a higher prevalence of liver cirrhosis, a higher SOFA score at diagnosis, and a more frequent presentation with severe sepsis or septic shock, but none of these differences reached statistical significance (Table 3). Ceftazidime-avibactam was prescribed as initial treatment in 40% of fatal (2/5) vs. 68.4% (13/19) of non-fatal episodes ($P = 0.33$). No difference in 90-day mortality was observed between episodes treated with ceftazidime-avibactam monotherapy vs. those treated with combination therapy (14.3% vs. 30%, $P = 0.62$).

Clinical cure was achieved in 62.5% of episodes (15/24). The causes of clinical failure at 30 days were death in two patients, persistence of symptoms and signs of infection in four patients, and recurrence of infection in a different location to the initial point in three patients. No differences in the clinical cure rate were found, taking into account patient comorbidities or based on the source of infection (Table 3). In addition, there were no differences between episodes in which ceftazidime-avibactam was used as the initial treatment or as salvage therapy (60% vs. 66.7%, $P = 1.00$), or between those treated with ceftazidime-avibactam monotherapy or combination therapy (64.3% vs. 60%, $P = 1.00$). In 20 episodes, ceftazidime-avibactam could be discontinued after infection cure (two of the 24 patients died before treatment was completed and in two patients the infection never reached cure status). Of these, seven (7/20, 35%) experienced a recurrence of the infection within 90 days of the end of treatment with ceftazidime-avibactam. The median time from the end of treatment to diagnosis of recurrence was 19 days (IQR 6–41). In two of these episodes, recurrence happened in the same location as the previous infection (a second pneumonia in a tracheostomy patient 19 days after treatment completion, and a recurrent surgical site infection of a foot amputation wound in a diabetic patient after 41 days). In contrast, five patients suffered a new infection caused by *OXA-48* CPE in a different location. The ceftazidime-avibactam MIC of the isolate was available in three recurrences; resistance (MIC > 8 mg/L) was not detected in any of them.

Four (16.7%) patients experienced adverse events during treatment with ceftazidime-avibactam that could be directly related to the drug. One patient suffered from mild, self-limited diarrhoea on the fourth day of treatment; another patient who died with ventilation-associated pneumonia showed progressive thrombocytopenia and cholestasis from the sixth day of treatment until death; and two patients showed neurological symptoms (myoclonus and encephalopathy, respectively), both associated with renal impairment, despite the fact that the ceftazidime-avibactam dosage had been adjusted based on manufacturer recommendations. In one of them, neurological symptoms disappeared after withdrawal of treatment whilst the other died within 48 hours due to uncontrolled infection.

4. Discussion

The present study examined a small cohort of patients with infection caused by *OXA-48* CPE treated with ceftazidime-avibactam. Based on the results, it was concluded that ceftazidime-avibactam is an effective and safe treatment for these infections, as proven by a 62.5% rate of clinical cure at 30 days of treatment onset, and 30-day and 90-day mortality rates of 8.3% and 20.8%, respectively.

Infections due to CPE are increasing globally, and mortality rates > 40% have been reported [13]. Previous studies had suggested that a combination of several active drugs, with carbapenem being part of the combination, is the most effective therapy [14,15]. However, toxicity of the available treatments and the emergence of CPE isolates showing decreased susceptibility to colistin and/or tigecycline further limit the therapeutic options. Recently published observational studies have demonstrated the efficacy of ceftazidime-avibactam for treating CPE [7-9,16-18]. Temkin

Table 3
Relationship of clinical and therapeutic variables with outcomes.

	Clinical failure (n = 9)	Clinical cure (n = 15)	*P*	90-day mortality (n = 5)	90-day survival (n = 19)	*P*
Age, mean (SD)	57.3 (12.3)	59.4 (17.8)	0.76	65.6 (6.5)	56.8 (16.9)	0.27
Male gender	8 (88.9)	12 (80.0)	1	4 (80.0)	16 (84.2)	1
Diabetes mellitus	2 (22.2)	5 (33.3)	0.67	1 (20.0)	6 (31.6)	1
Cardiovascular disease	5 (55.6)	3 (20.0)	0.10	2 (40.0)	6 (31.6)	1
Liver cirrhosis	2 (22.2)	1 (6.7)	0.53	2 (40.0)	1 (5.3)	0.1
Chronic renal failure	4 (44.4)	6 (40.0)	1	2 (40.0)	8 (42.1)	1
Chronic pulmonary disease	3 (33.3)	4 (26.7)	1	2 (40.0)	5 (26.3)	0.61
Solid organ/haematological cancer	1 (11.1)	4 (26.7)	0.61	1 (20.0)	4 (21.1)	1
Solid organ transplantation	4 (44.4)	2 (13.3)	0.15	0	6 (31.6)	0.28
Source						
Urinary	1 (11.1)	5 (33.3)	0.35	1 (20.0)	5 (26.3)	1
Respiratory	3 (33.3)	2 (13.3)	0.33	2 (40.0)	3 (15.8)	0.27
Osteoarticular/SST	1 (11.1)	3 (20)	1	0	4 (21.1)	0.54
Intraabdominal	4 (44.4)	3 (20)	0.36	2 (40)	5 (26.3)	0.61
Catheter	0	1 (6.7)	1	0	1 (5.3)	1
Meningitis	0	1 (6.7)	1	0	1 (5.3)	1
Charlson Comorbidity Index, mean (DS)	4.3 (2.0)	4.3 (3.4)	0.98	4.4 (2.9)	4.2 (3.0)	0.89
SOFA score, mean (DS)	4.9 (3.5)	2.4 (1.6)	0.07	5.0 (3.5)	2.9 (2.4)	0.13
Sepsis/septic shock	3 (33.3)	3 (20.0)	0.63	3 (60.0)	3 (15.8)	0.08
Bacteraemia	3 (33.3)	5 (33.3)	1	2 (40.0)	6 (31.6)	1
Appropriate treatment 24 h[a]	5 (55.6)	6 (40.0)	0.67	2 (40.0)	9 (47.4)	1
Appropriate treatment 48 h[b]	5 (55.6)	9 (60.0)	1	2 (40.0)	12 (63.2)	0.61
Initial treatment with C-A	6 (66.7)	9 (60.0)	1	2 (40.0)	13 (68.4)	0.33
C-A monotherapy	5 (55.6)	9 (60.0)	1	2 (40.0)	12 (63.2)	0.61
Days to appropriate treatment[c], mean (DS)	1.4 (1.9)	1.7 (1.7)	0.70	1.4 (1.3)	1.7 (1.8)	0.75
Days to C-A[d], mean (DS)	9.3 (14.6)	5.6 (4.2)	0.48	15.0 (18.2)	4.9 (4.1)	0.28
30-day mortality	2 (22.2)	0	0.13	N/A	N/A	
90-day mortality	4 (44.4)	1 (6.7)	0.05	N/A	N/A	

[a] Patients who received active treatment within 24 h of sample collection.
[b] Patients who received active treatment within 48 h of sample collection.
[c] Days from sample collection to receiving active treatment.
[d] Days from sample collection to receiving ceftazidime-avibactam
Abbreviations: SD, standard deviation; SST, skin-soft tissue; SOFA, sequential organ failure assessment; C-A, ceftazidime-avibactam.

et al. analysed 38 patients for whom ceftazidime-avibactam had been used as salvage therapy, and reported a clinical cure rate of 73.7% at the end of treatment and an in-hospital mortality rate of 39.5% [7]. However, 13 patients with infection due to *OXA-48* producers were included, and in this specific group, the mortality rate increased to 61.5%. Shields et al. reported a 30-day mortality and clinical cure rate of 24% and 59%, respectively, in a sample of 37 patients infected by carbapenem-resistant Enterobacteriaceae (CRE), of which mostly all (78%) were CPE (all of them KPC producers) [8]. In turn, King et al. described a series of 60 patients who received ceftazidime-avibactam for a CRE infection (presumably mainly due to KPC enzymes, although not explicitly stated) and reported an in-hospital mortality of 32% and clinical success rate of 65% [16]. Shields et al. found a 30-day mortality of 8% and clinical success rate of 85% in 13 patients with KPC-producing *Klebsiella pneumoniae* bacteraemia treated with ceftazidime-avibactam [17]. In a comparative analysis of patients with KPC-producing CRE infections initially treated with ceftazidime-avibactam (n = 38) vs. colistin (n = 99), van Duin et al. observed an adjusted 30-day mortality of 9% vs. 32%, respectively, and a 64% probability of achieving a better outcome in those treated with ceftazidime-avibactam [18]. Therefore, although the published experience in *OXA-48* CPE infections remains scarce, it is believed that the present study represents the largest series of patients to date in which ceftazidime-avibactam treatment has been evaluated, thus showing that its efficacy seems to be comparable to that observed in infections due to KPC producers.

In accordance to what has been described in previous studies [7-9], no differences in clinical cure (64.3% vs. 60%, $P = 1.00$) or 90-day mortality (14.3% vs. 30%, $P = 0.6$) rates were found between patients receiving ceftazidime-avibactam as monotherapy and those receiving it as combination therapy. This data stands in contrast to the data obtained from studies with other regimens [13,14,19-20] in which the combination of two or more in vitro active agents resulted in a lower mortality rate than that associated with active monotherapy, particularly in patients with the most severe infections. Monotherapy with ceftazidime-avibactam could presumably decrease the rate of adverse events, particularly acute kidney injury that is characteristic of treatments based on combinations with aminoglycosides or colistin [8,16]. Two (8.3%) of the current patients developed renal impairment during treatment. Further studies need to be carried out so as to determine whether combination therapy with ceftazidime-avibactam could improve prognosis of patients with serious CPE infections. The recurrence rate of infection at 90 days after the end of treatment was high (n = 7, 35%), which is similar to previous studies [8]. This probably reflects the high rate of persistent colonization despite appropriate systemic therapy.

This study had several limitations. First, the small sample of patients and retrospective and observational design hindered the ability to make definitive recommendations. Nonetheless, it is believed that the experience described here can provide additional reassurance that ceftazidime-avibactam may be an alternative that is as effective and far less toxic than the best options currently available. On the other hand, the MICs of successive cultures were not available in patients with persisting infection, hence why development of resistance as a cause of clinical failure cannot be ruled out.

In conclusion, this study examined a sample of patients with *OXA-48* CPE infections treated with ceftazidime-avibactam. Despite the small patient sample size, data suggest that it is effective and safe. Further studies with larger numbers of patients are needed to establish definitive recommendations for the optimal treatment of CPE infections and the role of ceftazidime-avibactam.

Declarations

Funding

None.

Competing Interests

None.

Ethical Approval

Not required.

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