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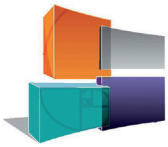

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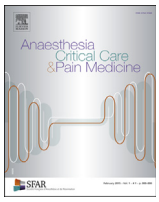

Original article

Use of aztreonam in association with cefepime for the treatment of nosocomial infections due to multidrug-resistant strains of *Pseudomonas aeruginosa* to β-lactams in ICU patients: A pilot study

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ABSTRACT

Objectives: Resistance to all β-lactams is emerging among *Pseudomonas aeruginosa* (PA) clinical isolates. Aztreonam and cefepime act synergistically in vitro against AmpC overproducing PA isolates. The objective of this study was to evaluate the clinical efficacy of this treatment in ICU patients infected with multidrug-resistant PA.
Material and methods: Retrospective study (2 years, 2 ICUs) in a tertiary university hospital. Inclusion criteria were proven infection with evidence of a bacterial strain of PA resistant to all β-lactams and treated with the association of at least aztreonam plus cefepime. Treatment was considered effective for pneumonia using CPIS scores at the end of treatment and for other infections, using the SOFA score and signs of infection improvement at the end of treatment. Infectious episodes were classified as cure or failure.
Results: Thirteen patients were included (10 nosocomial pneumonia, 3 nosocomial intra-abdominal infections). The median [25th–75th percentiles] admission SAPS2 score was 54 [51–69] and the median SOFA score at the beginning of infection was 7 [4–8]. The median CPIS scores for pneumonia at the beginning and end of treatment were 9 [7–10.5] and 2 [0.75–5.5]. The duration of treatment with the combination of aztreonam plus cefepime was 14 days [9.5–16]. Nine episodes were classified as cures and 4 as failures, indicating a clinical efficacy of 69.2%. Overall mortality was 38.5%.
Discussion: These data suggest that the association of cefepime plus aztreonam could be an attractive alternative in the treatment of infections with multidrug-resistant PA to all β-lactams with a clinical efficacy rate of 69%.

Nosocomial infections are associated with poor outcomes and increased costs, especially in the ICU. *Pseudomonas aeruginosa* is one of the most frequent bacteria isolated from nosocomial infections, especially for nosocomial pneumonia [1]. The bacterium has the capability to readily develop resistance to β-lactams, which is mainly due to chromosome-borne AmpC β-lactamase overexpression, and the loss of outer membrane porin OprD [2]. According to a previous in vitro study, aztreonam, which behaves as a "transient inhibitor" of Ambler class C β-lactamases [3], can restore the susceptibility to cefepime of AmpC overexpressing *P. aeruginosa* strains [4]. However, to the best of our knowledge, no clinical data on the effectiveness of this combination are currently available. The aim of this retrospective study was to evaluate the curative efficacy the aztreonam/cefepime combination against AmpC overexpressing *P. aeruginosa* infections in the ICUs.

1. Patients and methods

1.1. Study design

This was a retrospective study (2 ICUs of a tertiary referring centre) covering 2 years. The inclusion criterion was an infection

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due to AmpC overexpressing *P. aeruginosa* isolate resistant to all β-lactams that was treated with aztreonam in combination with cefepime. Patients treated for less than 5 days were not included. Only proven nosocomial pneumonia or intra-abdominal infections were included.

1.2. Treatment

Patients were treated with a standard intravenous dose of 2 g every 8 hours for aztreonam and 2 g every 8 hours for cefepime. This dosage was adapted according to creatinine clearance calculated with the Cockcroft formula. All patients were treated for documented infections. The initial protocol was set empirically to imipenem plus amikacin for pneumonia plus vancomycin for intra-abdominal infections according to local guidelines for nosocomial infections. Any additional treatment was left to the discretion of the physician, according to susceptibility testing. The duration of treatment was set a priori to 14 days.

1.3. Data collection

Demographics (age, gender) and the severity score, Simplified Acute Physiologic Score 2 (SAPS2), were collected on admission to the ICU [5]. At the time of infection diagnosis, the Sepsis-related Organ Failure Assessment (SOFA) Score [6], white blood cell (WBC) count and temperature were noted for all patients. For nosocomial pneumonia, a Clinical Pulmonary Infection Score (CPIS) was calculated [7]. Pneumonia was diagnosed when the CPIS $\geq$6. Protected tracheal suction (threshold 10^6 cfu/ml) or broncho-alveolar lavage (threshold 10^4 cfu/ml) were performed for microbiological diagnosis of pneumonia. A peroperative sample of peritoneal fluid was used for microbiological examination to diagnose intra-abdominal infection. At the end of treatment, SOFA scores, CPIS scores for pneumonia, white blood cell counts and temperature were noted. Patients were classified as success or failure according to their response to treatment (SOFA, CPIS, WBC and temperature). ICU outcomes were noted.

1.4. Microbiology

P. aeruginosa isolates were identified using MALDI-TOF mass spectrometry (Shimadzu, Marne-La Vallée, France). Antimicrobial susceptibility testing was performed by the disc diffusion method and interpreted according to EUCAST guidelines. MIC values of colistin were determined using E-test strips (Biomerieux, France). A phenotypic approach was carried out to identify the mechanisms of resistance as previously described [8]. This disc diffusion test uses eight phenotypic detection marker antibiotics to discriminate the wild-type β-lactam phenotype from the main acquired resistance patterns. This phenotypic approach is able to identify MexAB efflux system overexpression, acquired transmissible beta-lactamases, such as ESBLs and carbapenemases, chromosome-borne cephalosporinase overproduction, and loss of OprD porin.

1.5. Statistical analysis

Data are presented as medians with [25th–75th percentiles] or numbers (%). Initial quantitative parameters were compared with those at the end of treatment using a non-parametric Wilcoxon test for paired measures. A Mann-Whitney test was used to compare failure and success groups. $P < 0.05$ was considered significant.

2. Results

Thirteen patients were included (10 nosocomial pneumonia and 3 intra-abdominal infections). Individual demographics on ICU admission and at the onset of infections are presented in Table 1. The SAPS2 was 54 [51–69], age was 69 years old [49–74] and weight 81 kg [73–88]. At the time of diagnosis, the median SOFA score was 7 [4–8], CPIS score 9 [7–10.5], WBC count 16,800/mm^3 [12,800–19,850] and temperature 38.5 °C [37.4–38.8]. The median delay between hospital admission and infection was 40 days [7–112]. All the *P. aeruginosa* isolates that were recovered from lung or abdominal samples were intermediate or resistant to β-lactams, without restoration by calvulanate or tazobactam. According to the phenotypic characterization, all isolates were confirmed to over-express AmpC β-lactamase and to have lost OprD. Moreover, one isolate overproduced the MexAB and the MexXY system (7.7%). The susceptibility to main antimicrobial agents is presented in Table 2. The main characteristics of treatments and outcomes are exposed in Table 3. The individual dose of antimicrobial treatment was adjusted to the creatinine clearance of 57 ml/min [32.0–113.5]: aztreonam 57.7 mg/kg per day [52.9–69.8] and cefepime 57.5 mg/kg per day [31.8–71.9]. Eleven patients received for a short course (1 to 3 days) an aminoglycoside: 8 received amikacin and 2 received tobramycin. The median amikacin dose was 30.6 mg/kg [24–40] with a median plasmatic peak of 74.1 ml/l [44.0–95.6]. Five patients received additional inhaled colistin after availability of susceptibility testing (6 MUI per day). The duration

Table 1
Main characteristics of the patients on ICU admission and at the time of infection.

Patient	Gender	Infection	Age	Weight	SAPS2	Delay from hospital admission to infection	SOFA	CPIS	WBC count	Temperature (°C)
1	Male	NP	73	96	51	44	4	7	9800	38.2
2	Male	NP	30	87	37	72	8	12	14,100	38.5
3	Female	NP	84	89	74	14	8	10	10,000	38.5
4	Male	NP	65	104	70	48	1	9	20,700	38.2
5	Male	NP	69	81	54	23	8	9	30,200	37.8
6	Female	NP	20	82	51	40	2	12	16,800	40.5
7	Male	NP	72	70	69	104	4	7	26,600	36.2
8	Male	NP	69	76	54	41	4	6	13,600	37.0
9	Female	NP	84	81	56	7	7	7	16,800	36.3
10	Male	NP	75	55	25	62	8	9	12,000	38.5
11	Male	IAI	58	76	52	13	13	NA	17,700	39.6
12	Female	IAI	25	63	51	16	5	NA	16,700	38.9
13	Male	IAI	72	85	69	112	11	NA	19,000	38.7

NP: nosocomial pneumonia; IAI: intra-abdominal infection; SAPS: Simplified Acute Physiologic Score; SOFA: Sepsis Organ Failure Assessment Score; CPIS: Clinical Pulmonary Infection Score; WBC: white blood cells count; NA: not available; delay is expressed in days; WBC is expressed as number per mm^3.