

Brief report

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Ceftolozane-tazobactam for the treatment of ventilator-associated infections by colistin-resistant *Pseudomonas aeruginosa*

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ABSTRACT

The use of colistin for the treatment of multiresistant bacteria has led to the emergence of colistin-resistant strains of Gram-negative bacilli. Treatment of infections caused by these pan-drug-resistant bacteria is difficult owing to the paucity of effective antibiotics. We report two cases of ventilator-associated respiratory infection caused by pan-drug-resistant, colistin-resistant *Pseudomonas aeruginosa* that were successfully treated with ceftolozane-tazobactam.

Key words: Ceftolozane-tazobactam, colistin-resistant *Pseudomonas aeruginosa*, ventilator-associated respiratory infection, ICU

Ceftolozano-tazobactam en el tratamiento de infecciones respiratorias asociadas a ventilación mecánica por *Pseudomonas aeruginosa* resistente a colistina

RESUMEN

La utilización de colistina para el tratamiento de bacterias multirresistentes ha favorecido la aparición de cepas de bacilos gramnegativos resistentes a dicho antibiótico. El tratamiento de las infecciones producidas por estas bacterias panresistentes es difícil dada la escasez de antibióticos que se pueden emplear en esta situación. Se presentan dos pacientes con infecciones respiratorias relacionadas con ventilación mecánica producidas por una *Pseudomonas aeruginosa* panresistente y resistente a colistina que fueron tratadas con ceftolozano/tazobactam con buenos resultados.

Palabras clave: Ceftolozano/tazobactam, *Pseudomonas aeruginosa* resistente a colistina, infecciones respiratorias relacionadas con ventilación mecánica, UCI

INTRODUCTION

Ceftolozane is a new beta-lactam cephalosporin, whose mechanism of action is the same as that of other beta-lactams: it acts on penicillin-binding proteins and inhibits bacterial wall cell synthesis. Tazobactam has very limited antibacterial activity when administered in monotherapy. It inhibits various beta-lactamases, including broad-spectrum and extended-spectrum enzymes. Ceftolozane is active against *Escherichia coli*, *Morganella morganii*, *Proteus mirabilis*, *Serratia marcescens*, and *Salmonella* spp., as well as against non-fermenting Gram-negative bacilli especially *Pseudomonas aeruginosa*. It is the cephalosporin with the strongest activity against this pathogen, since it is stable in the presence of AmpC beta-lactamases and is not affected by the loss of outer membrane porins or by the presence of active efflux pumps. This new antibiotic is eliminated mainly via the kidneys, and its dose must be adjusted in patients with moderate to severe renal failure (estimated creatinine clearance <50 mL/min)¹. The efficacy of ceftolozane-tazobactam has been evaluated in adults in two pivotal phase III trials, and has been authorised for treatment of complicated abdominal infections and urinary tract infections, including pyelonephritis^{2,3}.

In recent years, the use of intravenous colistin to treat health care-related infections caused by non-fermenting Gram-negative bacilli, particularly *P. aeruginosa* and *Acinetobacter baumannii*, has led to the emergence of colistin-resistant strains⁴⁻⁶. Although the phenomenon is unusual, reports of infections caused by colistin-resistant Gram-negative bacilli treated with various combinations of antibiotics have shown different results^{7,8}. In February 2016, two consecutive patients admitted to the intensive care unit (ICU) of our hospital were diagnosed with ventilation-associated respiratory infections caused by pan-drug-resistant *P. aeruginosa*, which became resistant to colistin after treatment with this antibiotic and was susceptible to ceftolozane-tazobactam (MIC, 2 mg/L). Consequently, ceftolozane/tazobactam was requested through the

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compassionate use program of the Ministry of Health. In the present study, we report the characteristics of the patients, the infection, the pathogen isolated, and changes in the values of inflammatory markers and clinical signs of infection after administration of ceftolozane-tazobactam.

CASE REPORTS

Case 1. The patient was a 72-year-old man with no known drug allergies. He had a history of hypertension, diabetes mellitus, peripheral vascular disease with intermittent claudication, chronic obstructive pulmonary disease, and severe ventricular dysfunction caused by extensive necrosis affecting the inferior-lateral cardiac wall that required surgical revascularisation. He also had a 1-year history of arrhythmia due to atrial fibrillation. The patient attended the emergency department in January 2016 with rectal bleeding while taking anticoagulation therapy. Fibre-optic gastroscopy revealed a large clot in the fundus. The patient was intubated during the procedure owing to oxygen desaturation and hypotension and was admitted to the coronary intensive care unit (C-ICU) (APACHE II score, 28). Since the patient remained in cardiogenic shock after bleeding was controlled, pulmonary artery pressure was monitored and inotropic support provided. The clinical course was initially favourable, and inotropic and ventilatory support were withdrawn. Isolation of *P. aeruginosa* in the bronchial aspirate sample (BAS) on admission to the C-ICU was considered to indicate colonisation. After 18 days in the C-ICU, the patient went into hypovolaemic shock (serum haemoglobin, 4.5 g/dL) because of a bleeding ulcer in the antrum, which was resolved with no further complications. The patient also had tubular

necrosis, which was managed with renal replacement therapy (1 week). During the fourth week of stay in the C-ICU, the patient had symptoms of tracheobronchitis. Pan-drug-resistant *P. aeruginosa* was isolated from the BAS (table 1), and treatment with nebulised colistin (1 million IU t.i.d.) and meropenem (2 g b.i.d.) was started. Two weeks later, colistin-resistant strains of *P. aeruginosa* were isolated in surveillance samples (rectal swab). Owing to the failure of two attempted extubations, percutaneous tracheostomy was performed at 36 days after admission. Given the previous alteration in renal function and susceptibility to ceftolozane-tazobactam, treatment was started with this antibiotic at doses of 1/0.5 g t.i.d. (first four days), followed by 0.5/0.25 g t.i.d. for a further 10 days. The clinical and microbiological response was favourable, with negative BAS culture before withdrawal of treatment (colistin-susceptible *P. aeruginosa* persisted in the surveillance samples). Figure 1 shows changes in the values of inflammatory markers during treatment with ceftolozane-tazobactam. The patient was decannulated and moved to a conventional ward to continue treatment. He subsequently experienced refractory heart failure that did not respond to medical treatment and died three weeks after discharge from the C-ICU.

Case 2. The patient was a 48-year-old man with no known drug allergies. He had severe alcoholism with a history of hypertension, depressive syndrome, and dilated cardiomyopathy. In January 2016, he was admitted to the C-ICU from another hospital. He was already intubated and ventilated, with a diagnosis of respiratory insufficiency due to influenza A virus pneumonia (treated with oseltamivir, ceftriaxone, and levofloxacin) and haemodynamic instability (treated with vasoactive drugs [norepinephrine]). On admission (APACHE score,

Table 1 Antibiotic profile by date of isolation of *P. aeruginosa* in patients treated with ceftolozane-tazobactam

MIC (mg/L)	Patient 1		Patient 1		Patient 1		Patient 2		Patient 2		Patient 2	
	BAS		BAS		OR/Rectum		BAS		BAS		BAS	
	(January 20, 2016)		(February 11, 2016)		(February 23, 2016)		(January 24, 2016)		(February 5, 2016)		(February 19, 2016)	
Amikacin	≤ 8	S	≤ 8	S	16	I	≤ 8	S	16	I	≤ 8	S
Aztreonam	8	I	16	I	32	R	8	I	ND		8	I
Colistin	≤ 2	S	≤ 2	S	≥ 16	R	≤ 2	S	4	I	≤ 2	S
Ceftazidime	2	S	16	R	16	R	16	R	16	R	16	R
Ciprofloxacin	≤ 0,5	S	>2	R	≥ 4	R	>2	R	>4	R	>2	R
Cefepime	2	S	16	R	16	R	16	R	8	I	16	R
Gentamicin	2	S	>8	R	≥ 16	R	>8	R	≥16	R	>8	R
Imipenem	≤ 2	S	>8	R	≥ 16	R	>8	R	≥16	R	>8	R
Meropenem	≤ 2	S	>8	I	≥ 16	R	8	I	4	I	8	I
Piperacillin/tazobactam	≤ 8	S	64	R	≥ 12	R	32	R	≥128	R	32	R
Tobramycin	≤ 2	S	>8	R	≥ 16	R	>8	R	≥16	R	>8	R
Ceftolozane/tazobactam	ND		ND		2	S	ND		2	S	ND	

MIC, minimum inhibitory concentration; BAS, bronchial aspirate; OR, oropharyngeal; ND: not determined; S, susceptible; R, resistant; I, intermediate.

Acute phase reactants (Case 1)

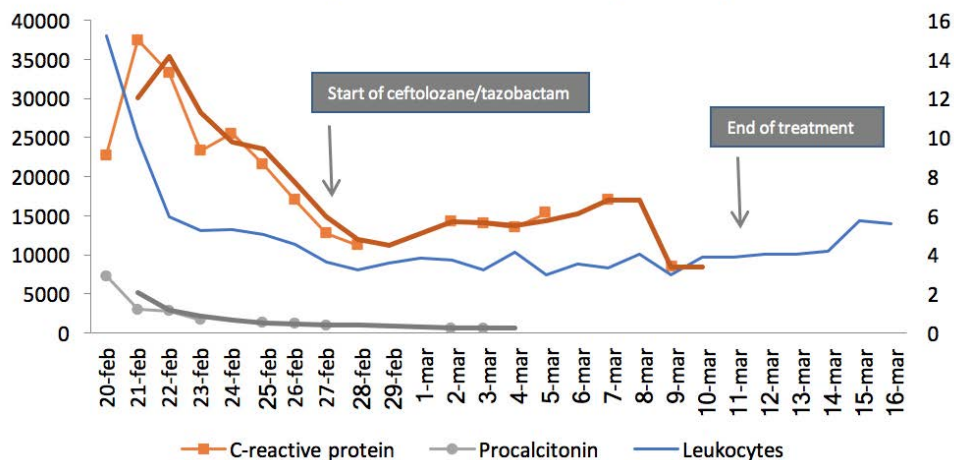


Figure 1 Inflammatory markers during treatment with ceftolozane/tazobactam (case 1)

Acute phase reactants (Case 2)

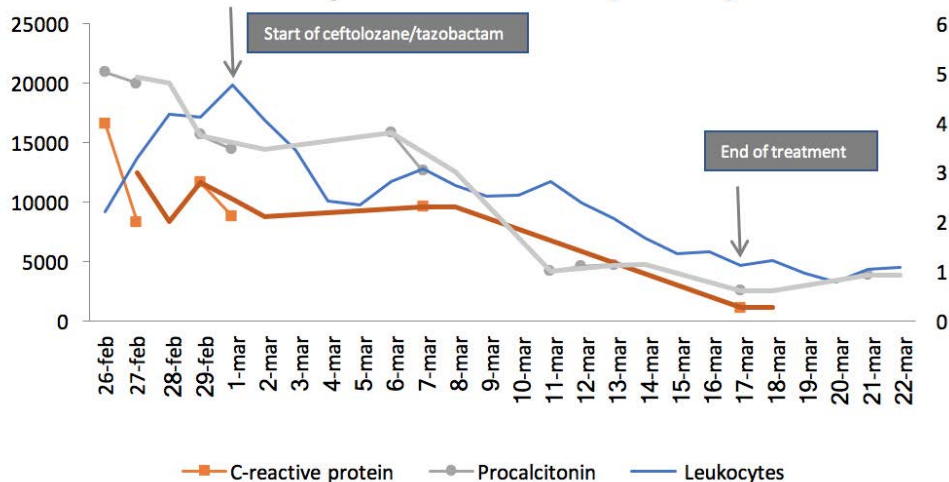


Figure 2 Inflammatory markers during treatment with ceftolozane/tazobactam (case 2)

23), he was monitored using transpulmonary thermodilution (PICCO®) owing to refractory hypotension and cardiogenic shock, which was treated with dobutamine. Echocardiography confirmed dilated cardiomyopathy with a severely depressed left ventricular ejection fraction, together with indirect signs of moderate pulmonary hypertension. The patient's clinical course improved gradually, and vasoactive support was withdrawn. Ten days after admission to the C-ICU, radiological signs worsened, with isolation of a new strain of pan-drug-resistant *P. aeruginosa* in a quantitative BAS culture ($> 10^6$ cfu/mL) (table 1), which was suggestive of ventilator-associated pneumonia. Therefore, treatment was started with nebulised colistin (1 million IU t.i.d.). Given the patient's poor clinical

condition and a chest computed tomography scan that revealed bilateral pulmonary opacities, signs of hepatisation, areas of necrosis, and air-fluid levels suggestive of lung abscesses, intravenous colistin was administered (3 million IU t.i.d.) in combination with aztreonam (2 g t.i.d.), meropenem (1 g t.i.d. in extended perfusion), and azithromycin (0.5 g per day). The patient's renal function deteriorated despite plasma colistin concentrations being within the therapeutic range (C_{\min} 1.8 mg/L at three days after intravenous administration), and extrarenal clearance techniques were applied because of persistent oligoanuria and anasarca. Percutaneous tracheostomy was performed 22 days after admission because of prolonged intubation. Culture of surveillance samples (rectum) and BAS

samples at 12 days after initiation of treatment with colistin revealed *P. aeruginosa* with a MIC of 4 mg/L. Given the altered renal values and persistence of multiple cavitated lesions on the computed tomography scan and after verifying *in vitro* susceptibility to ceftolozane-tazobactam (MIC, 2 mg/L) using microdilution techniques, administration of ceftolozane-tazobactam was started at doses of 0.5/0.25 g t.i.d. Treatment was maintained for 17 days. Subsequent culture of respiratory samples was negative, with good clinical evolution and a return to normal inflammatory marker values (figure 2). The patient subsequently presented with herpes simplex pneumonia, which was treated with acyclovir, and pseudomembranous colitis caused by *Clostridium difficile*, which was treated with oral vancomycin and metronidazole. The patient's clinical condition improved. After 87 days in the C-ICU, the patient was decannulated and transferred to the ward. Three months after discharge, colonisation by pan-drug-resistant, colistin-susceptible *P. aeruginosa* colonisation (surveillance samples [rectal swab]) persisted, but the patient's outcome was satisfactory.

DISCUSSION

Little experience has been reported with ceftolozane-tazobactam for treatment of infection in critically ill patients. Clinical trials to date have included patients with complicated abdominal and urinary infections^{2,3}, for which ceftolozane-tazobactam has been approved⁹. However, the number of critically ill patients included in the trials was very small. Data on ceftolozane-tazobactam in critically ill patients are limited to two studies, in which pharmacokinetic changes affecting the antibiotic are described in patients requiring extrarenal clearance techniques^{10,11}, and a letter to the editor¹² reporting three patients with respiratory insufficiency (two of whom had undergone tracheostomy) who developed nosocomial pneumonia caused by *P. aeruginosa* (no colistin-resistant strains) and were successfully treated with colistin.

The patients here described differ from those in clinical trials, and the antibiotic studied was not administered for infections approved in the summary of product characteristics⁹. We provide data on two patients who had spent long periods in the C-ICU with major comorbidities (especially cardiovascular comorbidities), failure of two or more organs at admission, and acute respiratory insufficiency of different causes. The patients also required treatment with mechanical ventilation and underwent tracheostomy between the second and third week of stay owing to prolongation of ventilation. During their stay, they were diagnosed with several health care-associated infections, which were treated with various combinations of antibiotics. The first patient presented with ventilator-associated tracheobronchitis. Pan-drug-resistant, colistin-susceptible *P. aeruginosa* was isolated in the tracheal aspirate and treated using inhaled antibiotic therapy. The clinical response was good. Colistin-resistant strains were identified in surveillance samples (rectal or oropharyngeal swab) on day 12. The second patient was in the room next to that of the first patient and had ventilator-associated pneumonia caused by multire-

sistant *P. aeruginosa* (susceptible to colistin and amikacin). He received intravenous colistin for 26 days and nebulised colistin for 36 days and developed resistance to the drug. In this case, colistin induced acute renal failure that required renal replacement therapy. In both cases, susceptibility testing of both antibiotics against the pan-drug-resistant strain of *P. aeruginosa* revealed an MIC₉₀ for ceftolozane-tazobactam of 2 mg/L. The drug was then requested through the compassionate use program of the Ministry of Health.

Ceftolozane-tazobactam was administered intravenously to both patients as a 30-minute bolus (500/250 mg t.i.d.) for at least two weeks. In both cases, the dose administered was higher than the dose recommended in the summary of product characteristics for approved indications, taking into account renal function and the application of extrarenal clearance techniques. The dose was that used in a clinical trial evaluating ceftolozane-tazobactam for the treatment of nosocomial pneumonia¹³, namely, 2 g of ceftolozane and 1 g of tazobactam t.i.d. (results forthcoming). The clinical and microbiological response was excellent in both cases: culture of BAS was negative, although the surveillance samples indicated the presence of colonisation. No adverse effects were recorded, and renal function recovered in the second patient. Antibiotic therapy was continued.

Our experience shows that ceftolozane-tazobactam could be suitable for the treatment of colistin-resistant *P. aeruginosa* or pan-drug-resistant, colistin-susceptible strains of *P. aeruginosa* in patients with kidney failure or a high risk of kidney failure.

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