

New antimicrobial alternatives in the treatment of pneumonia

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Ceftobiprole medocaril

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ABSTRACT

Ceftobiprole medocaril is a broad-spectrum 5th-generation cephalosporin with activity against Gram-positives such as methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*, and against Gram-negatives such as *Pseudomonas aeruginosa*. The recommended dose is 500 mg every 8 h in 2-hour infusions. Various clinical trials have demonstrated its usefulness in the treatment of community-acquired pneumonia and nosocomial pneumonia, with the exception of ventilator-associated pneumonia. In summary, it is a very useful antibiotic for the treatment of pneumonia.

Keywords: Ceftobiprole; antibiotic; multidrug-resistance; pneumonia

INTRODUCTION

One of the pandemics facing the world in the 21st century is that of superbugs and antimicrobial resistance. Infections by these superbugs could be responsible for millions of deaths in the coming decades. For this reason, the scientific community has been making a great effort for some time in the development of new antibiotics to face this great challenge. The result of this effort has been the appearance of new drugs, among which is ceftobiprole medocaril.

Pneumonia is the infection with the highest morbidity and mortality. It mainly impacts the extremes of life due to the special vulnerability during childhood and old age. Ceftobiprole medocaril is a new antibiotic for the treatment of pneumonia with a different antimicrobial profile than its predecessors.

MICROBIOLOGICAL PROFILE

Ceftobiprole medocaril is a 5th generation cephalosporin (pyrrolidinone-3-ylidene-methyl cephalosporin) for parenteral use that has extended activity against Gram-negatives such as *Pseudomonas aeruginosa* or 85% of enterobacteria, and against Gram-positives such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, and *Enterococcus faecalis*, among others. Ceftobiprole is generally not active against microorganisms that cause atypical pneumonia [1].

Ceftobiprole medocaril is capable of inhibiting cell growth through its binding to penicillin-binding proteins (PBPs), which hinders cell wall synthesis and induces bacterial death.

In relation to Gram-positives, its activity against MRSA is due to its union with the extended narrow groove of the PBP2a and its affinity to other staphylococcal PBPs (PBP1, PBP3 and PBP4). In the case of its activity against penicillin-resistant *S. pneumoniae*, it is mainly explained by its great affinity for PB-P2b and PBP2x, unlike other beta-lactams such as ceftriaxone. Finally, its action against *E. faecalis* is due to its high affinity for enterococcal PBP [2].

Ceftobiprole is active against Gram-negatives such as *P. aeruginosa* and enterobacteria. It loses its efficacy against enterobacteria that express carbapenemases, Ambler's Class A β -lactamases such as extended spectrum β -lactamases (ES-BLs), or AmpC β -lactamase types. It is active against *P. aeruginosa* due to its binding to PBP3 and loses its efficacy when it expresses metallo-carbapenemases (IMP and VIM) and D (OXA-10), carbapenemases or Ambler's Class A β -lactamases including ESBLs.

Finally, it is also active against some anaerobic bacteria such as *Clostridium* spp. and *Fusobacterium* spp. but not against others such as *Bacteroides* spp., *Prevotella* spp. and *Veillonella* spp.

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Table 1		Main outcomes of randomized clinical trials of ceftobiprole in community-acquired pneumonia and hospital-acquired pneumonia.		
CAP	Ceftobiprole	Ceftobiprole ± linezolid	95% CI of the difference	
Clinical cure				
CE patients	200/231 (86.6)	208/238 (87.4)	-6.9, 5.3	
ITT patients	240/314 (76.4)	257/324 (79.3)	-9.3, 3.6	
Patients receiving i.v. therapy only	77/103 (74.8)	73/101 (72.3)	-9.6, 14.6	
Switch to oral therapy	123/128 (96.1)	135/137 (98.5)	-6.4, 1.5	
Microbiological eradication				
ME patients	60/68 (88.2)	69/76 (90.8)	-12.6, 7.5	
Microbiological ITT	70/87 (80.5)	79/97 (81.4)	-12.4, 10.4	
HAP	Ceftobiprole	Ceftazidime/linezolid	95% CI of the difference	
Clinical cure				
CE patients	174/251 (69.3)	174/244 (71.3)	-10, 6.1	
HAP (excluding VAP)	154/198 (77.8)	141/185 (76.2)	-6.9, 10	
VAP	20/53 (37.7)	33/59 (55.9)	-36.4, 0	
HAP (excluding VAP), mechanically ventilated	21/38 (55.3)	15/37 (40.5)	-7.6, 37.1	
ITT patients	195/391 (49.9)	206/390 (52.8)	-10, 4.1	
HAP (excluding VAP)	171/287 (59.6)	167/284 (58.8)	-7.3, 8.8	
VAP	24/104 (23.1)	39/106 (36.8)	-26, -1.5	
HAP (excluding VAP), mechanically ventilated	21/69 (30.4)	19/70 (27.1)	-11.8, 18.3	
Microbiological eradication				
ME patients	87/162 (53.7)	106/170 (62.4)	-19.2, 1.9	
HAP (excluding VAP)	73/116 (62.9)	81/120 (67.5)	-16.7, 7.6	
VAP	14/46 (46)	25/50 (50)	-38.8, -0.4	
Microbiological ITT	105/269 (39)	127/267 (47.6)	-16.9, -0.2	
HAP (excluding VAP)	87/179 (48.6)	97/181 (53.6)	-15.3, 5.3	
VAP	18/90 (20)	30/86 (34.9)	-27.9, -1.9	

CAP, community-acquired pneumonia; CE, clinically evaluable; CI, confidence interval; HAP, hospital-acquired pneumonia; ITT, intention-to-treat; ME, microbiologically evaluable; VAP, ventilator-acquired pneumonia.

PHARMACOLOGICAL FEATURES

The recommended dose of ceftobiprole medocaril is 500 mg every 8 h in 2-hour infusions and is rapidly (<1 min) and almost completely converted to active ceftobiprole. The peaks of the active principle in the blood are reached 30 minutes after the start of the infusion. It has a low protein binding (approximately 16% and independent of concentration in the range of 0.5-100 mg/L) and a distribution volume of around 18-20/L [3].

At the recommended dose in subjects with normal renal function for a minimum inhibitory concentration (MIC) of 4 mg/L, the probability of achieving an MIC \leq 50% was 80%. Ceftobiprole is eliminated almost exclusively in the urine with about 88% of the administered dose recovered in urine. In patients with a creatinine clearance of 30-50 mL/min, it is rec-

ommended to space the dose every 12 hours. With creatinine clearance <30 mL/min, the dose will be reduced to 250 mg/12 h. Ceftobiprole has few drug interactions because it does not inhibit cytochrome P450 [4,5].

CLINICAL EXPERIENCE

There are two pivotal clinical studies of ceftobiprole medocaril conducted in 638 patients with community-acquired pneumonia and 781 patients with nosocomial pneumonia [6,7]. The first of them was performed in patients with CAP who required hospitalization. Patients were randomized 1:1 to ceftobiprole 500 mg every 8 h in 2-hour infusions versus ceftriaxone 2 g every 24 h in 30-minute infusions and stratified by pneumonia severity index (PSI). If there was suspicion of MRSA,

linezolid 600 mg every hour was associated in the ceftriaxone group and placebo in the ceftobiprole group. The primary endpoint was the clinical cure rate at the test of cure (TOC) visit (in both the ITT and CE populations). Secondary outcomes were microbiological eradication at TOC visit, clinical cure according to PSI, and pneumonia-specific mortality at 30 days. A total of 314 patients (ITT) were included in the ceftobiprole group and 324 in the ceftriaxone group, of which CE were 231 and 238, respectively. Regarding the main outcome, ceftobiprole treatment was found to be non-inferior to comparator treatment in both the ITT and CE populations (Table 1). In patients with PSI class IV-V, the cure rates also did not show differences (secondary outcome) between the ceftobiprole group and the comparator. Likewise, no differences were found according to microbiological etiology. In relation to microbiological eradication, the results were similar and no significant differences were observed (Table 1). Lastly, there were no deaths in the ceftobiprole group versus two in the ceftriaxone group. All this without notable security or tolerance problems.

The second study was conducted in patients with hospital-acquired pneumonia (HAP) [7]. In this case, patients were randomized 1:1 to ceftobiprole 500 mg every 8 h in 2-hour infusions versus ceftazidime 2 g every 8 h plus linezolid 600 mg every 12 h. A total of 781 patients were included, 391 in the ceftobiprole group (251 CE) and 390 in the ceftazidime/linezolid group (244 CE). The main outcome under study was again the clinical cure rate at the TOC visit (in both the ITT and CE populations). The main secondary outcome included microbiological eradication. Non-inferiority was demonstrated in the treatment of HAP with ceftobiprole versus ceftazidime/linezolid in both the CE and ITT populations (Table 1). However, this failed to demonstrate the non-inferiority of ceftobiprole in the subgroup of patients with ventilator-associated pneumonia (VAP). Very similar results were found for the secondary outcome, demonstrating non-inferiority for microbiological eradication of ceftobiprole with the exception of the VAP subgroup. There were no significant differences in mortality or safety and tolerability between the two treatment groups.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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