Official journal of the Spanish Society of Chemotherapy

Update on antimicrobial pharmacotherapy

Ceftobiprole: a clinical view

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Revista Española de Quimioterapia
doi:10.37201/req/s01.09.2021

ABSTRACT

Ceftobiprole is a broad-spectrum, fifth-generation cephalosporin currently approved for community-acquired and non-ventilator-associated hospital-acquired pneumonia. High bactericidal and anti-biofilm activity has been exhibited in *in vitro* and animal models. This, together with its synergism with other antibiotics against gram-positive bacteria, makes it an ideal candidate for treatment of complex infections, such as those associated with devices or infective endocarditis. More clinical data are needed to achieve drug positioning.

Keywords: ceftobiprole, MRSA, synergy, anti-biofilm.

Ceftobiprole is a broad-spectrum, fifth-generation cephalosporin, currently approved for community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) excluding ventilator-associated one [1,2]. This drug exerts potent bactericidal activity against several gram-positive and gram-negative pathogens, as well as *Streptococcus* spp. (including most *Enterococcus faecalis*) and *Staphylococcus* spp. [including methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative *Staphylococcus* (CNS)], *Haemophilus influenzae*, *Moraxella catarrhalis*, most of the *Enterobacterales* group, and *Pseudomonas aeruginosa* (Table 1). On the other hand, ceftobiprole shows reduced or no activity against *Enterococcus faecium*, *Proteus vulgaris*, most Gram-negative anaerobes, *Acinetobacter baumannii*, *Burkholderia cepacian* complex, and *Stenotrophomonas maltophilia*. With respect to difficult-to-treat bacteria, ceftobiprole has activity against derepressed AmpC producers, but not against extended-spectrum β-lactamases (ESBLs), carbapenemases or metallocarbapenemase-producing *Enterobacterales*. Epidemiological surveillance studies have shown excellent susceptibility rates (close to 100%) in *S. aureus*, MRSA, CNS, *S. pneumoniae* and *E. faecalis*, although with more discreet results in *Enterobacterales* and *P. aeruginosa*. With respect to the latter, ceftobiprole susceptibility rates of about 70% were reported in a recent international cohort that included 1064 isolates [3,4]. To our knowledge, there are no published data concerning the susceptibility of *P. aeruginosa* to ceftobiprole in Spanish isolates, although in a recent conference communication, only 59% of 95 Spanish isolates tested were susceptible. A limitation is that we do not know which hospitals participated in that study and that may have conditioned these results [5]. Ceftobiprole shows several pharmacokinetic and pharmacodynamic properties that make it a very interesting molecule: high bactericidal activity, proven in experimental models (*in vitro* and animal studies), low protein binding (16%), a high volume of distribution, and predominantly renal excretion (70-90%). Consequently, concentrations of ceftobiprole found in feces after 7 days of therapy are very low, as was demonstrated in a study in healthy volunteers [6]. This may be associated with a low rate of *Clostridioides difficile* infection [1,2].

The data sheet recommends 500 mg every 8 hours administered as a 2-hour intravenous infusion, demonstrating linear pharmacokinetics if higher doses than usual are used. It exhibits two very promising features that may help to place it in a wide range of complex infections in the near future. First, it shows *in vitro* synergy with different antibiotics, highlighting combinations with daptomycin against MRSA, and with piperacillin/tazobactam and amikacin against *P. aeruginosa* [7,8]. Second, it has very good activity against biofilm, once again showing synergy with rifampin and vancomycin [9]. These characteristics could make it an excellent option against MRSA or CNS infective endocarditis, endovascular or prosthesis-related infections, osteomyelitis, among others. While the clinical data about the efficacy of ceftobiprole in these scenarios has increased in recent years, it is not easy to draw solid conclusions because it has been used in most cases as combined or

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Table 1 **Spectrum of ceftobiprole compared with other antimicrobials**

	Staphylococcus aureus		Coagulase negative staphylococci	*Streptococcus pneumoniae*		*Pseudomonas aeruginosa*		*Enterobacterales*	
	MSSA	MRSA		Non-MDR	MDR /PRSP	CAZ-S	CAZ-R	Non-ESBL	ESBL
Ceftobiprole									
Ceftaroline									
Cefepime									
Ceftazidime									
Ceftriaxone									
Meropenem									
Pip/tazobactam									
Linezolid									
Daptomycin									
Vancomycin									

MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *S. aureus*; MDR: multidrug resistant; PRSP: penicillin-resistant *Streptococcus pneumoniae*; CAZ: ceftazidime; S: susceptible; R: resistant ESBL: extended-spectrum β-lactamases; Pip/tazobactam: Piperacillin/ tazobactam

salvage therapy [10-13]. There are some ongoing clinical trials, such as the one establishing the efficacy and safety of ceftobiprole versus daptomycin in the treatment of *S. aureus* bacteremia, including infective endocarditis [14].

Ceftobiprole is generally well tolerated with a low rate of adverse effects. The most common ones are dysgeusia, nausea, vomiting, and diarrhea, although hyponatremia and myoclonus have also been reported on rare occasions [1,2,11].

In our opinion, the use of ceftobiprole as empirical treatment in nosocomial infections is limited because the number of *P. aeruginosa*-susceptible strains is not well established in our media and because it has no activity against ESBLs strains. Own susceptibility data are needed for the adequate positioning of the drug in this regard. Nevertheless, ceftobiprole may have a role as targeted therapy to carry out antimicrobial diversification in nosocomial infections, replacing standard combinations such as ceftazidime plus and vancomycin. It could also be useful as salvage therapy in combination with daptomycin in MRSA infections, although comparisons with other combination options, such as daptomycin plus fosfomycin, or daptomycin plus fosfomycin are needed. Preliminary data shows that ceftobiprole is at stable for up to 24 hours at 25ºC and protected from light, which also allows for potential administration in outpatient parenteral antimicrobial therapy [15].

In the meantime, we look forward to more observational studies and data from clinical trials that will help us to establish definitively new indications for ceftobiprole.

CONFLICTS OF INTEREST

LELC has served as scientific advisor for Angelini, speaker for Angelini, ViiV, Gilead and Correvio, and has served as trainer for ViiV. PMMPC declare no clonflic of interest.

REFERENCES

1. Nicholson SC, Welte T, File TM Jr, Strauss RS, Michiels B, Kaul P, et al. A randomised, double-blind trial comparing ceftobiprole medocaril with ceftriaxone with or without linezolid for the treatment of patients with community-acquired pneumonia requiring hospitalisation. Int J Antimicrob Agents. 2012;39(3):240-6. doi: 10.1016/j.ijantimicag.2011.11.005.
2. Awad SS, Rodriguez AH, Chuang YC, Marjanek Z, Pareigis AJ, Reis G, Scheeren TW, Sánchez AS, Zhou X, Saulay M, Engelhardt M. A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clin Infect Dis. 2014;59(1):51-61. doi: 10.1093/cid/ciu219.
3. Pfaller MA, Flamm RK, Duncan LR, Streit JM, Castanheira M, Sader HS. Antimicrobial activity of ceftobiprole and comparator agents when tested against contemporary Gram-positive and -negative organisms collected from Europe (2015). Diagn Microbiol Infect Dis. 2018; 91(1):77-84. doi: 10.1016/j.diagmicrobio.2017.12.020.
4. Stephen Hawser, Ian Morrissey, Nimmi Kothari, Nowel Redder. Susceptibility of Gram-positive and Enterobacterales clinical isolates isolated during 2018 from France, Germany, Italy, Spain and the United Kingdom [Abstract 3940]. European Congress of the Clinical Microbiology and Infectious Diseases; Paris. 2020.
5. Stephen Hawser, Ian Morrissey, Nimmi Kothari, Noëlle Jemmely. Ceftobiprole susceptibility of European Gram-positive and Enterobacteriaceae Clinical Isolates from different infection sources collected in 2018 [Abstract 3921]. European Congress of the Clinical Microbiology and Infectious Diseases; Paris. 2020.

6. Bäckström T, Panagiotidis G, Beck O, Asker-Hagelberg C, Rashid MU, Weintraub A, Nord CE. Effect of ceftobiprole on the normal human intestinal microflora. Int J Antimicrob Agents. 2010;36(6):537-41. doi: 10.1016/j.ijantimicag.2010.07.021.

7. Campanile F, Bongiorno D, Mongelli G, Zanghì G, Stefani S. Bactericidal activity of ceftobiprole combined with different antibiotics against selected Gram-positive isolates. Diagn Microbiol Infect Dis. 2019;93(1):77-81. doi: 10.1016/j.diagmicrobio.2018.07.015.

8. Kresken M, Körber-Irrgang B, Läuffer J, Decker-Burgard S, Davies T. In vitro activities of ceftobiprole combined with amikacin or levofloxacin against *Pseudomonas aeruginosa*: evidence of a synergistic effect using time-kill methodology. Int J Antimicrob Agents. 2011;38(1):70-5. doi: 10.1016/j.ijantimicag.2011.01.028.

9. Abbanat D, Shang W, Amsler K, Santoro C, Baum E, Crespo-Carbone S, Lynch AS. Evaluation of the in vitro activities of ceftobiprole and comparators in staphylococcal colony or microtitre plate biofilm assays. Int J Antimicrob Agents. 2014;43(1):32-9. doi: 10.1016/j.ijantimicag.2013.09.013.

10. Zhanel GG, Kosar J, Baxter M, Dhami R, Borgia S, Irfan N, et al. Real-life experience with ceftobiprole in Canada: Results from the CLEAR (Canadian LEadership on Antimicrobial Real-life usage) registry. J Glob Antimicrob Resist. 2021; 24:335-339. doi: 10.1016/j.jgar.2021.01.014.

11. Durante-Mangoni E, Andini R, Mazza MC, Sangiovanni F, Bertolino L, Ursi MP, Paradiso L, Karruli A, Esposito C, Murino P, Corcione A, Zampino R. Real-life experience with ceftobiprole in a tertiary-care hospital. J Glob Antimicrob Resist. 2020;22:386-390. doi: 10.1016/j.jgar.2020.03.010.

12. Tascini C, Attanasio V, Ripa M, Carozza A, Pallotto C, Bernardo M, et al. Ceftobiprole for the treatment of infective endocarditis: A case series. J Glob Antimicrob Resist. 2020;20:56-59. doi: 10.1016/j.jgar.2019.07.020.

13. Mahmoud E, Al Mansour S, Bosaeed M, Alharbi A, Alsaedy A, Aljohani S, et al. Ceftobiprole for treatment of MRSA blood stream infection: A case series. Infect Drug Resist. 2020;13:2667-2672. doi: 10.2147/IDR.S254395.

14. Hamed K, Engelhardt M, Jones ME, Saulay M, Holland TL, Seifert H, Fowler VG Jr. Ceftobiprole versus daptomycin in *Staphylococcus aureus* bacteremia: a novel protocol for a double-blind, Phase III trial. Future Microbiol. 2020;15(1):35-48. doi: 10.2217/fmb-2019-0332.

15. Jimidar I, Vermeersch H, Tinke A, Hickey MB, Golea DJ. Stability of ceftobiprole medocaril powder for injection in common fluids and containers [abstract P-54E]. American Society of Health-System Pharmacists; Seattle, WA, 8-11 June 2008.