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Original article

In vitro activity of ceftobiprole on 440 *Staphylococcus aureus* strains isolated from bronchopulmonary infections

Activité in vitro du céftobiprole sur 440 souches de Staphylococcus aureus *isolées d'infections broncho-pulmonaires en France*

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Abstract

Objective. – We assessed the in vitro activity of ceftobiprole on 440 *Staphylococcus aureus* clinical strains isolated from bronchopulmonary infections (2010–2014).

Methods. – *S. aureus* isolates were characterized for methicillin resistance, PVL status, and clonal complex. All isolates were tested for minimal inhibitory concentrations (MIC) determination by broth microdilution method for ceftobiprole, ceftaroline fosamil, and comparator antibiotics (linezolid, tigecycline, vancomycin, and daptomycin).

Results. – A total of 325 (74%) strains were methicillin-susceptible *S. aureus* (MSSA) and 115 (26%) were methicillin-resistant *S. aureus* (MRSA); 105 (24%) *S. aureus* strains were PVL-positive, including 35.2% (37/105) MRSA and 64.8% (68/105) MSSA. Ceftobiprole was highly active against *S. aureus* with MIC_{90} of 1 mg/L, MICs ranging between 0.12 and 4 mg/L (only one resistant strain, MIC of 4 mg/L). MIC_{50} and MIC_{90} were twice lower in MSSA than MRSA. Moreover, PVL^+ MRSA were slightly more susceptible to ceftobiprole (MIC_{50} of 0.5 mg/L and MIC_{90} of 1 mg/L) than PVL^- MRSA (MIC_{50} and MIC_{90} of 1 mg/L). The ceftobiprole-resistant strain was also resistant to ceftaroline fosamil and presented the D239L mutation in PBP2A. The comparator antibiotics were equally active on the strains tested, with MIC_{90} of 0.5 mg/L for ceftaroline fosamil, tigecycline, and daptomycin; 1 mg/L for vancomycin; and 2 mg/L for linezolid.

Conclusions. – Our results suggest that ceftobiprole is highly active against *S. aureus* and is an effective alternative to vancomycin or linezolid in the management of staphylococcal pneumonia. However, close monitoring of isolates should be maintained to prevent resistant strain diffusion.

Keywords: Ceftaroline fosamil; Ceftobiprole; Bronchopulmonary infections; *Staphylococcus aureus*

Résumé

Objectifs. – Nous avons testé l'activité in vitro du céftobiprole sur une série française de 440 souches de *Staphylococcus aureus*, toutes isolées d'infections broncho-pulmonaires entre 2010 et 2014.

Méthodes. – Nous avons utilisé une méthode par microdilution pour déterminer les concentrations minimales inhibitrices (CMI) de céftobiprole, céftaroline, linézolide, tigécycline, vancomycine et daptomycine, et avons recherché la résistance à la méticilline et le portage de la PVL.

Résultats. – Nous avons recensé 325 (74 %) *S. aureus* sensibles à la méticilline (SASM), 115 (26 %) résistants (SARM) et 105 porteurs de la PVL, dont 68 SASM et 37 SARM. Le céftobiprole était très actif sur *S. aureus*, avec une CMI_{90} de 1 mg/L. Une seule souche était résistante avec une CMI de 4 mg/L, également résistante à la céftaroline. Les SARM présentaient des CMI_{50} et CMI_{90} au céftobiprole deux fois supérieures à

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celles des SASM. Les SARM porteurs de la PVL y étaient légèrement plus sensibles que les SASM non porteurs (CMI_{50} à 0,5 mg/L et 1 mg/L, respectivement). Les autres antibiotiques anti-staphylococciques testés étaient également actifs sur *S. aureus*, avec des CMI_{90} à 0,5 mg/L pour céftaroline, tigécycline et daptomycine, 1 mg/L pour vancomycine et 2 mg/L pour linézolide.

Conclusions. – Le céftobiprole est très actif sur *S. aureus* et constitue une bonne alternative à la vancomycine ou au linézolide dans les pneumopathies staphylococciques. Cependant, il est important de suivre l'évolution de cette sensibilité au cours du temps afin de détecter l'émergence et la diffusion des souches résistantes.

Mots clés : Céftaroline ; Céftobiprole ; Infections broncho-pulmonaires ; *Staphylococcus aureus*

1. Introduction

Ceftobiprole medocaril is the prodrug form of ceftobiprole, a new subclass of cephalosporin with an activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative bacteria. Just like other β-lactams, ceftobiprole blocks peptidoglycan cell wall synthesis by binding to penicillin-binding proteins (PBPs). The peculiar characteristic of ceftobiprole is its high affinity for PBP2a, involved in methicillin resistance of *S. aureus*. Ceftobiprole has recently been approved in Europe for the treatment of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) (excluding ventilator-associated pneumonia) in adults, where the incriminating pathogens are multidrug-resistant [1].

S. aureus is a major pathogen in humans, responsible for various types of infections, including pneumonia [2]. In France, *S. aureus* pneumonia accounts for 12.6% of CAP [3] and a large proportion of HAP [4]. An early effective treatment is essential for *S. aureus* pneumonia management, and affects patient outcomes [5]. Moreover, some *S. aureus* strains producing Panton-Valentine leukocidin (PVL) can induce life-threatening necrotizing pneumonia, which urgently requires both bactericidal and antitoxin treatment against *S. aureus* [6].

Several studies have shown that ceftobiprole was very effective against pathogens isolated from hospitalized patients, including *S. aureus* and MRSA [7–10]. Nevertheless, it is essential to monitor the antimicrobial activity of ceftobiprole on bacteria involved in bronchopulmonary infection (which is the on-label indication of ceftobiprole), and notably on *S. aureus* and MRSA isolated in a country-specific setting, to detect potential changes in susceptibility pattern.

We aimed to study the in vitro activity of ceftobiprole on 440 *S. aureus* clinical strains, all isolated from bronchopulmonary infections in French patients between 2010 and 2014. *S. aureus* isolates were characterized for methicillin resistance, PVL status, and clonal complex (CC) to then analyze the susceptibility to ceftobiprole in various *S. aureus* genotypes.

2. Materials and methods

2.1. Bacterial strains

A total of 440 *S. aureus* strains were selected among French Staphylococci National Reference Center (Staphylococci NRC, Lyon, France) collections from 2010 to 2014. All *S. aureus* strains were isolated from respiratory infections, in French clinical laboratories, and sent to the Staphylococci NRC, either because of clinical severity of symptoms or because of particular antibiotic resistance patterns. Thirty-three per cent of *S. aureus* strains were isolated from tracheal aspirates, 26% from bronchoalveolar lavage fluid, 20% from sputum (including 8% from cystic fibrosis patients), 9% from pleural effusion, 8% from blood culture during pneumonia, and 4% from lung biopsy and abscesses. Species identification was confirmed at the Staphylococci NRC by MALDI-TOF (Matrix-Assisted Laser Desorption/Ionization-Time of Light) mass spectrometry, VitekMS (BioMérieux®). *S. aureus* strains were stored at –20 °C. All isolates were characterized using *S. aureus* Genotyping Kit 2.0 Alere Technologies GmbH (Jena, Germany). When needed, the *mecA* gene was sequenced as previously described [11].

2.2. Susceptibility testing method

All isolates were tested for minimal inhibitory concentration (MIC) determination by broth microdilution method using validated commercially prepared panels, Sensititre Trek Diagnostic Systems, Life Technologies Europe (Naerum, Denmark), in Mueller-Hinton broth for ceftobiprole, ceftaroline fosamil, and comparator antimicrobial agents (linezolid, tigecycline, vancomycin, and daptomycin). Susceptibility interpretation was based on EUCAST breakpoints [12].

3. Results

3.1. Epidemiological distribution of S. aureus strains isolated from bronchopulmonary infections

Among the 440 *S. aureus* strains isolated from bronchopulmonary infections, 325 (74%) were methicillin-susceptible *S. aureus* (MSSA) and 115 (26%) were methicillin-resistant *S. aureus* (MRSA), based on *mecA* gene presence. No *mecC* was detected among all selected strains. With regard to PVL status, 105 (24%) *S. aureus* strains carried *luk-PV* gene, 35.2% were MRSA strains (37/105) whilst 64.8% (68/105) were MSSA strains.

With regard to the genetic background, 216 strains (49.9%) belong to the agr1 group, 106 strains (24.5%) to agr2, 91 strains (21.0%) to agr3, and 20 strains (4.6%) to the agr4 group. Overall, *S. aureus* clustered within 26 clonal complexes; most isolates clustered into the CC8 (69/440, 15.7%), CC5 (61/440, 13.9%),