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Original article

Interpreting carbapenem susceptibility testing results for *Pseudomonas aeruginosa*

Interprétation des tests de sensibilité aux carbapénèmes de Pseudomonas aeruginosa

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Abstract

Objectives. – Carbapenems are among the most powerful antipseudomonal agents. Limited data is available on drug susceptibility testing by routine methods (disc diffusion and Etest) for meropenem and doripenem. We aimed to compare the in vitro activity of imipenem, meropenem, and doripenem against *Pseudomonas aeruginosa*.

Methods. – A total of 311 *P. aeruginosa* strains isolated from respiratory specimens in 170 patients who developed ventilator-associated pneumonia in two intensive care units were collected over a period of 31 months. The susceptibility of these isolates to imipenem, meropenem, and doripenem were determined by Etest and disc diffusion method.

Results. – Considering either all isolates or only the first isolates recovered per patient (311 and 170 respectively), the susceptibility rate for doripenem was higher than that for meropenem and imipenem. When MICs determined by Etest were converted into interpretative categories (S, I, R) using French (CA-SFM) guidelines, a poor correlation was observed for meropenem and doripenem. The percentages of correlation with the disc diffusion method were 90.6% and 89.7% for imipenem, 80.5% and 82.6% for meropenem, and 80.5% and 73.3% for doripenem, for the first isolates and all isolates, respectively. The rate of minor errors was as high as 17.7% and 16.1% for meropenem and 17.7% and 25.7% for doripenem for the first isolates and all isolates, respectively.

Conclusion. – The accuracy of disc diffusion using CA-SFM guidelines appears unsatisfactory for all three carbapenems justifying guideline update for *P. aeruginosa* and carbapenems.

Keywords: Antimicrobial susceptibility testing; Breakpoints; Carbapenems; *Pseudomonas aeruginosa*

Résumé

Objectifs. – Les bêtalactamines, dont les carbapénèmes, sont les antibiotiques les plus actifs contre *Pseudomonas aeruginosa.* Peu d'études ont été réalisées sur les tests de sensibilité par diffusion et Etest du méropénème et du doripénème. L'objectif était de comparer l'activité in vitro de l'imipénème, du méropénème et du doripénème contre *P. aeruginosa*.

Méthodes. – Nous avons mesuré la sensibilité aux carbapénèmes (imipénème, méropénème et doripénème) de 311 souches de *P. aeruginosa*, responsables de pneumopathies acquises sous ventilation mécanique (PAVM), isolées sur une période de 31 mois dans deux unités de réanimation. La sensibilité de ces isolats a été déterminée par diffusion en milieu gélosé et par Etest.

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Résultats

L'interprétation des CMI a mis en évidence un pourcentage de souches sensibles plus important pour le doripénème que pour le méropénème et l'imipénème. La concordance complète entre la méthode de diffusion en milieu gélosé et par Etest était de 90,6 % et 89,7 % pour l'imipénème, 80,5 % et 82,6 % pour le méropénème, et 80,5 % et 73,3 % pour le doripénème, pour les premiers isolats de PAVM et l'ensemble des isolats respectivement. La corrélation entre les deux méthodes est donc faible pour le méropénème et le doripénème, et ceci est principalement du fait d'erreurs mineures (17,7 % et 16,1 % pour le méropénème et 17,7 % et 25,7 % pour le doripénème pour les premiers isolats et l'ensemble des isolats respectivement).

Conclusions. – Ces résultats montrent l'importance de l'application des recommandations EUCAST pour *P. aeruginosa* et les carbapénèmes.

Mots clés : Tests de sensibilité aux antibiotiques ; Concentrations critiques ; Carbapénèmes ; *Pseudomonas aeruginosa*

1. Introduction

Pseudomonas aeruginosa is one of the main organisms responsible for hospital-acquired infections, such as urinary tract infections and ventilator-associated pneumonia (VAP) [1,2]. Only a few antibiotics are available for the treatment of *P. aeruginosa* infections as this bacterium is naturally multidrug resistant due to the combination of impermeability, multiple efflux systems, and a chromosomal AmpC β-lactamase. *P. aeruginosa* can also develop acquired resistance to many antibiotics (cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, etc.) [3,4]. Three of the four available carbapenems, i.e. imipenem, meropenem, and doripenem, are among the most powerful antipseudomonal agents. The spectrum of activity of these carbapenems differs; doripenem – a recently approved parenteral 1β-methylcarbapenem – being more active against Gram-positive bacteria than meropenem and more active against Gram-negative bacteria than imipenem [5,6]. Meropenem and doripenem have recently been marketed and limited data is available on the interpretation of susceptibility tests using EUCAST and CA-SFM (European Committee on Antimicrobial Susceptibility Testing and Antibiogram Committee of the French Society for Microbiology, respectively) breakpoints and the correlation of results yielded by the two methods widely used for in vitro susceptibility testing on agar, i.e. disc diffusion method and MIC determination by Etest. We aimed to compare the results obtained for imipenem, meropenem, and doripenem against *P. aeruginosa* using both methods.

2. Materials and methods

2.1. Bacterial strains

Consecutive isolates (n = 311) of *P. aeruginosa* were prospectively collected by the laboratory of bacteriology at the Pitié-Salpêtrière Hospital (Paris, France) over a period of 31 months (January 2009 to July 2011). These isolates were obtained from the respiratory specimens of 170 patients who developed *P. aeruginosa* VAP in two intensive care units. Fifty-six (33%) patients had at least one VAP recurrence, defined as the persistence or reappearance of clinical and biological signs of infection and significant concentrations of *P. aeruginosa* in lower respiratory tract specimens at least two days (but no more than 28 days) after completing antibiotic therapy for the first episode. A total of 311 isolates have been studied: 170 from the first episode of VAP and 141 from the subsequent episodes. After collection, the strains were frozen and stored for future analysis.

P. aeruginosa CIP 76110 (ATCC 27853) was used as control.

2.2. Antimicrobial susceptibility testing

The susceptibilities of the isolates to imipenem, meropenem, and doripenem were determined by disc diffusion method (Biorad®, Marnes-la-Coquette, France) according to the guidelines of the CA-SFM, as follows: overnight cultures on agar, suspension in distilled water to reach a turbidity equivalent to that of a 0.5 McFarland standard, then diluted to 1/10, inoculation of Mueller-Hinton agar plates (Biorad®) by swabbing, incubation for 18 hours at 37 °C. The discs containing 10 μg doripenem, meropenem, and imipenem were supplied by Biorad®.

MICs of the carbapenems were determined by Etest (bioMérieux®, Marcy l'Étoile, France) on Mueller-Hinton agar using the manufacturer's instructions. Etest MIC values were rounded up to the nearest two-fold dilution.

MIC results were also interpreted according to the 2013 guidelines of the CA-SFM (Table 1). These guidelines recommend the same breakpoints as EUCAST for each of the three carbapenems (Table 1).

2.3. Result analysis

The minimum concentrations of antibiotic required to inhibit the growth of 50% and 90% of the isolates tested (MIC_{50} and MIC_{90}, respectively) were calculated for each agent.

The correlation between interpretative categories based on disc diffusion method and Etest was evaluated for the isolates of the first episodes (n = 170) and for all isolates (n' = 311). MICs yielded by the latter were used as reference. A very major error (VME) was defined as susceptibility by agar diffusion method but resistance by Etest, a major error (ME) as resistance by agar diffusion method but susceptibility by Etest, and a minor error (mE) as intermediate susceptibility by one method and

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