Brief Communication

Assessment of Doripenem, Meropenem, and Imipenem against Respiratory Isolates of *Pseudomonas aeroginosa* in a Tertiary Care Hospital of North India

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Abstract

Objective: *Pseudomonas aeruginosa* is one of the leading pathogen causing healthcare-associated infections, particularly in immunocompromised and critically ill patients. The development of carbapenem resistance in *P. aeruginosa* infections is worrisome. Data specifically comparing the susceptibility of the three available carbapenems are lacking in the Indian subcontinent. **Materials and Methods:** We evaluated the minimum inhibitory concentrations (MICs) of the three commonly used carbapenems– imipenem, meropenem, and doripenem against, 435 *P. aeruginosa* isolates obtained from respiratory samples and compared their susceptibility patterns to determine the best possible carbapenem among those available that may be used in combination regimes. **Results:** Overall, 222 (51.0%) of isolates were susceptible to doripenem followed by imipenem 206 (47.3%) and meropenem 195 (44.8%), respectively. Two hundred and sixty-two (60.23%) strains were intermediate or resistant to at least one carbapenem. The MIC_{90} of all three carbapenems was >32 μg/ml while the MIC_{50} of meropenem was 16 μg/ml which was higher than MIC_{50} of both imipenem (4 μg/ml) and doripenem (2 μg/ml). **Conclusion:** Our study revealed that doripenem exerted better *in vitro* activity against the tested bacteria compared to imipenem and meropenem, but the difference was not statistically significant.

Keywords: Doripenem, imipenem, meropenem, minimum inhibitory concentration, *Pseudomonas aeruginosa*

Introduction

Pseudomonas aeruginosa is one of the leading pathogens causing healthcare-associated infections particularly in immunocompromised and the critically ill patients. It is one of the most prevalent pathogens in nosocomial pneumonia, especially in patients with high-risk factors such as mechanical ventilation or catheter intubation. It has been acquiring multidrug resistance (MDR) at an alarming rate, raising much clinical concern as effective antimicrobial agents are limited and dwindling.[1] The development of carbapenem resistance, against *P. aeruginosa* infections is worrisome.[2]

Carbapenem resistance can be due to the production of enzymes, such as AmpC or a metallo-β-lactamase; overexpression of efflux pumps; porin deficiencies; or target site alterations. One of the major risk factors for carbapenem resistance is carbapenem use itself resulting in selective pressure on bacterial populations.[3]

Literature suggests, doripenem is an antipseudomonal carbapenem that has greater *in vitro* activity against *P. aeruginosa* isolates than other carbapenems and is less likely to select for carbapenem-resistant strains under experimental conditions.[4,5] Its 1-β-methyl side chain provides resistance to dehydropeptidase so that this molecule does not require the addition of cilastatin for protection from this enzyme. It is also remarkably stable after reconstitution, increasing the opportunity for prolonged infusion. The recommended dosing for doripenem is 0.5 g every 8 h (administered through 1 or 4 h infusions).[5]

Doripenem has been described as having the favorable attributes of both imipenem and meropenem against both Gram-positive and Gram-negative bacteria.[6] Data

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specifically comparing the susceptibility of the three available carbapenems are lacking. Therefore, we evaluated the minimum inhibitory concentrations (MICs) of the three commonly used carbapenems; imipenem, meropenem, and doripenem against isolates of *P. aeruginosa* obtained from respiratory samples and compared their susceptibility patterns.

Materials and Methods

This prospective study was conducted in the Department of Microbiology at a tertiary care referral hospital of North India from August 2015 to September 2016. We studied *in vitro* susceptibility of 435 *P. aeruginosa* isolates recovered from respiratory samples against carbapenems; imipenem, meropenem, and doripenem. These samples included sputum, endotracheal aspirate (ETA), bronchoalveolar lavage (BAL), and mini BAL from patients with suspected respiratory tract infections. The samples were processed semiquantitatively, and colony counts of 10^5 CFU/ml were taken as pathogenic. Samples that yielded *P aeruginosa* identified using standard techniques[7] and confirmed by an automated identification system (Phoenix™ 100, BD Biosciences, Maryland, USA) were included for further study.

Antimicrobial susceptibility testing and determination of MIC for the 3 carbapenems was done on Mueller Hinton agar using E-test strips (AB Bio Merieux, France). The interpretation was done according to Clinical and Laboratory Standards Institute (CLSI) guidelines[8] and results were compared with European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.[9] *P. aeruginosa* strains were classified as MDR, extensively drug-resistant (XDR), and pandrug resistant (PDR), according to the classification proposed by Magiorakos *et al*.[10]

Results

A total of 435 *P. aeruginosa* were isolated from respiratory samples comprising 216 (49.66%) sputum, 208 (47.82%) ETA, 10 (2.30%) BAL, and 1 (0.23%) mini BAL. One hundred and forty-one (32.41%) of the samples were polymicrobial. 15.40% (67) of the isolates were MDR, 42.99% (187) were XDR, and 1.61% (7) were PDR while the remaining 40% (174) isolates were sensitive to carbapenems. Overall 222 (51.0%) of isolates were susceptible to doripenem followed by imipenem 206 (47.3%) and meropenem 195 (44.8%), respectively. Two hundred and sixty-two (60.23%) strains were intermediate or resistant to at least one carbapenem.

Carbapenem MIC distributions (MIC_{50} and MIC_{90}) for these strains are given in Table 1. Doripenem MICs were lower than those of imipenem or meropenem. The MIC_{90} of all three carbapenems was >32 μg/ml while the MIC_{50} of meropenem was 16 μg/ml which was higher than MIC_{50} of both imipenem (4 μg/ml) and doripenem (2 μg/ml). MIC_{50} of meropenem, imipenem, and doripenem was significantly different (P = 0.002). A diagrammatic representation of the cumulative MIC values of imipenem, meropenem, and doripenem has been depicted in Figure 1. We also evaluated doripenem sensitivity in imipenem and meropenem nonsusceptible isolates [Table 2]. Among the doripenem-resistant isolates (n = 204), 10 (4.9%) were sensitive to imipenem, 1 (0.4%) was sensitive to meropenem, and 8 (3.9%) were sensitive to both imipenem and meropenem. With respect to the meropenem-resistant isolates (n = 233), 11 (4.7%) were sensitive to imipenem, 20 (8.6%) were sensitive to doripenem, and 8 (3.4%) were sensitive to both imipenem and doripenem. Of the 216 imipenem-resistant isolates, 3 (1.3%) were sensitive to meropenem, 22 (10.1%) were sensitive to doripenem, and 6 (2.7%) were sensitive to both meropenem and doripenem as shown in Table 2. On comparing susceptibility results of imipenem, meropenem, and doripenem using CLSI and EUCAST breakpoints, there was no significant change in the sensitivity rate of meropenem (195; 44.8% by CLSI vs. 194; 44.6% by EUCAST). However, in case of imipenem, the sensitivity by CLSI was 206 (47.3%) while that by EUCAST was 218 (50.1%). Similarly, 222 (51.0%) isolates were sensitive to doripenem by CLSI while 205 (47.5%) were sensitive by EUCAST. This difference of sensitivities in case of imipenem and doripenem was not statistically significant (P = 0.60, 0.90, 0.37 for imipenem, meropenem and doripenem, respectively). There were 3 (0.69%) isolates in case of imipenem, 15 (3.5%) in case of meropenem and 14 (3.2%) in case of doripenem which fell within the gap between the defined range of sensitive and resistant and hence remained unclassified, as there is no intermediate category defined in EUCAST.

Discussion

Treatment options for resistant *P. aeruginosa* infections are restricted, and combination therapy with other antimicrobial

Table 1: Carbapenem minimum inhibitory concentration distribution of *Pseudomonas aeruginosa*

Antibiotic	Range	MIC_{50}	MIC_{90}
Meropenem	0.019->32	16	>32
Imipenem	0.04->32	4	>32
Doripenem	0.012->32	2	>32

MIC_{50} of meropenem doripenem and imipenem is significantly different (P=0.002). MIC: Minimum inhibitory concentration

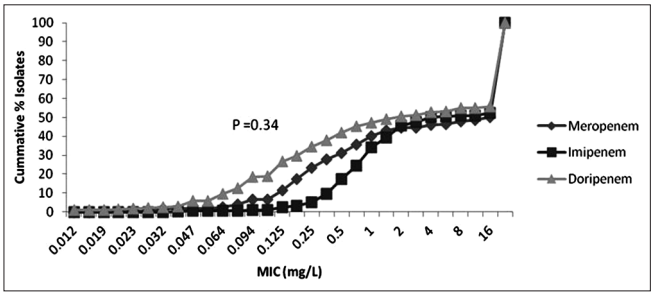

Figure 1: Distribution of cumulative percentage isolates and minimum inhibitory concentrations of doripenem, meropenem, and imipenem among *Pseudomonas aeruginosa* isolates

Table 2: Correlation of sensitivities of carbapenems

Antibiotic resistance	Imipenem sensitive (%)	Meropenem sensitive (%)	Doripenem sensitive (%)	Imipenem + doripenem sensitive (%)	Meropenem + imipenem sensitive (%)	Doripenem + meropenem sensitive (%)
Doripenem resistant (*n*=204)	10 (4.9)	1 (0.4)	-	-	8 (3.9)	-
Meropenem resistant (*n*=233)	11 (4.7)	-	20 (8.6)	8 (3.4)	-	-
Imipenem resistant (*n*=216)	-	3 (1.3)	22 (10.1)	-	-	6 (2.7)

Meropenem vs Doripenem (*P* value = 0.0754); Imipenem verses Doripenem (*P* value = 0.37)

agents has been suggested time and again as a potential management strategy. In particular, synergism between colistin/carbapenem has been demonstrated in several studies despite the apparent resistance of *P. aeruginosa* to carbapenems.[1] However, the comparative data regarding the susceptibility of *P. aeruginosa* to the available carbapenems is lacking worldwide. Hence, this study was undertaken as it is imperative to determine the best possible carbapenem among those available that may be used in combination regimes.

In this study, 60.23% (262) of *P. aeruginosa* strains responsible for respiratory infections at our hospital were intermediate-susceptible or resistant to at least one of the carbapenems; imipenem, meropenem, or doripenem. This is much higher than the isolates studied by Luyt *et al*.[4] who found 40% of their isolates were resistant.

We also found that in our isolates MICs of doripenem were lower than imipenem or meropenem MICs [Table 1 and Figure 1] although the difference was not statistically significant in case of MIC_{90}, MIC_{50} of meropenem, imipenem, and doripenem showed a significant difference ($P = 0.002$). This is similar to several other studies.[4,11,12] In a study by Luyt *et al*.,[4] similar results were found with respect to the MICs, but their difference was statistically significant both in case of MIC_{90} and MIC_{50}, implying that doripenem was clearly superior to the other two carbapenems with regard to *P aeruginosa*. Hu *et al*.[1] studied only multidrug-resistant *P aeruginosa* isolates with a high percentage of carbapenem resistance and found that doripenem still performed better than the other two carbapenems *in vitro*. In an Indian study by Goyal *et al*.[13] also, doripenem had an 84.2-fold lower MIC towards *P. aeruginosa* isolates (0.38 mg/L) than meropenem (>32 mg/L). One reason why doripenem is more potent than meropenem and imipenem might be due to its higher affinity for penicillin-binding protein (PBP2) and PBP3 in *P. aeruginosa*.[14] In contrast, in a study conducted by Bretonnière *et al*.,[11] MIC values of meropenems were lower than to the other two carbapenems.

In our study, the MIC range (mg/L) was; 0.012–>32 for doripenem, 0.04–>32 for imipenem and 0.019–>32 for meropenem. This is similar to several other studies.[15-17] In the present study MIC_{50} and MIC_{90} data also revealed doripenem to be the most active carbapenem tested against *P. aeruginosa* clinical isolates. However, MIC_{50} and MIC_{90} of doripenem (2 and >32 mg/L, respectively) were higher than those reported from previous studies.[4,13,16] Similar findings were seen in MIC_{50} and MIC_{90} of imipenem and meropenem. This may be due to the antibiotic selection pressure promoted by inappropriate dosage and duration of the carbapenems.

In our study, 8.6% of *P. aeruginosa* isolates tested as nonsusceptible to meropenem were susceptible to doripenem and 10.1% imipenem resistant isolates were sensitive to doripenem. This is interestingly higher than the pioneer study conducted by Pillar *et al*.[17] In their study, 13% of *P. aeruginosa* isolates tested as nonsusceptible to imipenem, were susceptible to doripenem. This may be due to OprD mutations, often involved in resistance to imipenem but not for meropenem or doripenem which is usually due to increased efflux or production of β lactamases. However, the mechanisms of resistance in Pseudomonas are complex, and several mechanisms may be involved simultaneously.[11] When we compared susceptibility results of meropenem and imipenem with doripenem using CLSI, EUCAST breakpoints, no significant variations in sensitivities were seen. This is in concordance with several other studies.[14,18]

Conclusion

The high rate of drug resistance in *P. aeruginosa* is alarming, and it is crucial to screen for carbapenem resistance prior initiation of antibiotic therapy. Our study revealed that although doripenem exerted better *in vitro* activity against the tested bacteria compared to imipenem and meropenem, the difference was not statistically significant. However, in few isolates, as demonstrated in our study, susceptibility test to one carbapenem could not predict susceptibility to the other drugs in this class, and hence, the MIC for each carbapenem should be determined separately in resistant/intermediate MIC when facing a potentially difficult to treat infection especially in resourceful settings. MIC values can help in guiding the clinicians to use combination therapy or higher/more frequent recommended dosing of carbapenems.

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Conflicts of interest

There are no conflicts of interest.

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