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# COMPARISON OF IN VITRO ACTIVITY OF DORIPENEM, IMIPENEM AND MEROPENEM AGAINST CLINICAL ISOLATES OF ENTEROBACTERIACEAE, PSEUDOMONAS AND ACINETOBACTER IN SOUTHERN POLAND

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In the study we tested drug sensitivity to 3 carbapenems (doripenem, imipenem and meropenem) of Gram-negative clinical isolates from Southern Poland.
**Material and methods.** 89 strains were examined: 42 from Pseudomonas genus, 16 Acinetobacter baumannii strains and 31 Enterobacteriaceae strains. Etests were used according to the producers instructions, MIC values were interpreted using EUCAST criteria.
**Results.** Highest in vitro activity against Pseudomonas spp. was shown for doripenem, then meropenem and the lowest for imipenem (MIC values were definitely lower for doripenem; differences were statistically significant); A. baumannii strains showed similar sensitivity to doripenem, meropenem and imipenem (differences non-significant); all Enterobacteriaceae strains showed sensitivity to the tested antimicrobials.
**Conclusions.** As a conclusion–doripenem, which has high in vitro activity (almost the same as imipenem and meropenem) as well as beneficial pharmacologic properties, may be an alternative solution in the treatment of multiresistant Gram-negative bacteria, especially in patients in severe status who require restrictive antibiotic regimens.
**Key words:** doripenem, imipenem, meropenem, Enterobacteriaceae, Pseudomonas, Acinetobacter

Carbapenems from the 2nd group are drugs of choice in severe nosocomial infections caused by multiresistant Gram-negative bacteria. Recently, besides of the well-known agents, imipenem and meropenem, doripenem is being introduced on a wider scale. Advantages of doripenem include good pharmacologic properties, especially good stability in the infusion fluid. A study called Comparative Activity of Carbapenem Testing (COMPACT) has ended recently, with the objective to evaluate sensitivity of Gram-negative bacteria to 3 carbapenems of group 2 (doripenem, imipenem and meropenem). Thus far results of drug sensitivity testing are available from Western Europe mainly, while results from Central and Eastern Europe were not reported separately.

The objective of this study was to compare the activity of three carbapenems (doripenem, imipenem and meropenem) against clinical isolates of Gram-negative bacteria from Southern Poland.

## MATERIAL AND METHODS

Strains that were examined were collected from wound swabs, sputum, bronchoalveolar lavage (BAL) or blood of patients with complicated abdominal or blood infections or hospital

acquired pneumonia (HAP) including ventilator-associated pneumonia (VAP). Patients were hospitalized on intensive care units (ICU) and other departments of the following hospitals: Dietl Specialistic Hospital in Cracow, St. John Grande Hospital of the Merciful Brothers' Order in Cracow and the Voivodeship Hospital in Kielce. Collection of strains used in the study are microorganisms gathered from May 2010 till December 2011.

Identification of strains was performed using API 20 E (bioMerieux) for Enterobacteriaceae and API 20 NE (bioMerieux) for non-fermenting bacteria from Pseudomonas and Acinetobacter genera. Presence of Extended Spectrum ß-lactamase (ESBL) in Enterobacteriaceae was confirmed using the double-disc method. Sensitivity to tested drugs (doripenem, imipenem and meropenem) was tested using the Etests according to producer's recommendations (bioMerieux). Interpretation of MIC values was based on EUCAST criteria. Quality control was done using the E. coliATCC 25922, K. pneumoniae ATCC 700603 and P. aeruginosa ATCC 27853 reference strains.

The MIC values were analysed for the given strain groups using the matched pairs test with nonparametric Wilcoxon signed-rank statistics. This procedure was chosen because of extremely askew data distribution which couldn't be transformed into Gausian distribution. In such a case more conservative parametric tests are inappropriate. The matched pairs analysis was found to be the most convenient for comparison of the data series for concordant pairs. In all statistical tests $p<0.05$ was considered significant. All analyses were conducted with the SAS JMP 7.0 package.

## RESULTS

89 strains were used in the study, including 42 Pseudomonas spp. strains (40 P. aeruginosa strains: 44.94% of all strains; 2 P. oryzihabitans strains: 2.25%), 16 Acinetobacter baumannii strains (17.97%), 31 Enterobacteriaceae strains (34.84%).

38 strains (42.7% of all strains) were collected from ICU patients, the remaining 51 strains were collected from patients hospitalized in departments other than ICU (57.3%).

Most strains were isolated from patients with HAP (72 strains – 80.9% of all strains), 30 strains (33.7% of all strains) came from patients suffering from VAP. 23 strains (25.8%) were collected from patients with complicated abdominal infections and only 5 strains were isolated from blood (5.6%)

12 examined strains were ESBL-positive (13.5% of all strains).

The most commonly isolated species of Enterobacteriaceae was Klebsiella pneumoniae (9 strains – 30%), then E. coli (7 strains – 23.4%) and E. cloacae (4 strains – 13.3%).

The highest in vitro activity against Pseudomonas spp. was demonstrated for doripenem (71.43% of sensitive strains), then meropenem (64.29%) and the smallest for imipenem (52.38%). A. baumannii strains showed the same sensitivity to doripenem, meropenem and imipenem (87.5% of A. baumannii were sensitive). All Enterobacteriaceae strains showed sensitivity to tested antibiotics (tab. 1, 2, 3, 4).

In case of Pseudomonas spp. and Acinetobacter baumanni, MIC comparison was done for the given carbapenem pairs and the percentages of strains with MIC for one given

Table 1. Comparison of doripenem activity for ICU and non-ICU strains

| Doripenem | Type of department | Number of strains | $MIC_{50}$ | $MIC_{90}$ |
|---|---|---|---|---|
| All strains | ICU | 38 | 0,09 | 1,50 |
| | non-ICU | 51 | 0,19 | 3 |
| *Pseudomonas* spp. | ICU | 19 | 0,25 | 4 |
| | non-ICU | 23 | 0,25 | 3 |
| *Acinetobacter baumannii* | ICU | 7 | 0,5 | 0,75 |
| | non-ICU | 9 | 0,5 | 8 |
| *Enterobacteriaceae* | ICU | 11 | 0,02 | 0,02 |
| | non-ICU | 19 | 0,02 | 0,08 |
| Enterobacteriaceae with ESBL | ICU | 9 | 0,02 | 0,03 |
| | non-ICU | 3 | 0,03 | 0,41 |
| Enterobacteriaceae without ESBL | ICU | 2 | 0,02 | 0,02 |
| | non-ICU | 16 | 0,01 | 0,03 |

Table 2. Doripenem activity against tested strains

| | MIC range | $MIC_{50}$ | $MIC_{90}$ | % sensitive strains | % intermediate strains | % resistant strains |
|---|---|---|---|---|---|---|
| All strains | 0,008-12 | 0,19 | 2,2 | 84,27 | 11,24 | 4,49 |
| *Pseudomonas* spp. | 0,008-8 | 0,25 | 3,9 | 71,43 | 23,81 | 4,76 |
| *Acinetobacter baumannii* | 0,008-3 | 0,5 | 4,5 | 87,5 | 0 | 12,5 |
| *Enterobacteriaceae* | 0,012-0,75 | 0,02 | 0,05 | 100 | 0 | 0 |

Table 3. Imipenem activity against tested strains

| | MIC range | $MIC_{50}$ | $MIC_{90}$ | % sensitive strains | % intermediate strains | % resistant strains |
|---|---|---|---|---|---|---|
| All strains | 0,094-32 | 0,5 | 12 | 75,28 | 8,99 | 15,73 |
| *Pseudomonas* spp. | 0,094-24 | 1 | 12 | 52,38 | 19,05 | 28,57 |
| *Acinetobacter baumannii* | 0,094-32 | 0,63 | 6,5 | 87,5 | 0 | 12,5 |
| *Enterobacteriaceae* | 0,094-0,75 | 0,19 | 0,25 | 100 | 0 | 0 |

Tabela 4. Aktywność meropenemu względem badanych szczepów
Table 4. Meropenem activity against tested strains

| | MIC range | $MIC_{50}$ | $MIC_{90}$ | % sensitive strains | % intermediate strains | % resistant strains |
|---|---|---|---|---|---|---|
| All strains | 0,008-32 | 0,25 | 12 | 84,27 | 0 | 15,73 |
| *Pseudomonas* spp. | 0,012-32 | 0,44 | 15,6 | 64,29 | 7,14 | 28,57 |
| *Acinetobacter baumannii* | 0,008-24 | 0,75 | 4,5 | 87,5 | 0 | 12,5 |
| *Enterobacteriaceae* | 0,012-0,75 | 0,02 | 0,05 | 100 | 0 | 0 |

carbapenem which was lower, equal or higher than MIC for the second given carbapenem, were compared (tab. 5). MIC values for Pseudomonas strains for doripenem were significantly lower than for imipenem and meropenem (but for the latter doripenem's vantage was smaller); when comparing the activities of imipenem and meropenem, the activity of meropenem was higher. The situation was different for Acinetobacter baumanni. Among the classic carbapenems imipenem was more active than meropenem. The activity of doripenem was higher than meropenem and comparable to imipenem.

For all strains the differences in the distribution of MIC values were statistically significant ($p<0.0001$ with doripenem vs imipenem as well as doripenem vs meropenem comparisons, $p=0.0002$ with imipenem vs meropenem comparison).

In case of Pseudomonas spp. strains, the differences in MIC values distribution were statistically significant for doripenem vs imipenem or meropenem ($p<0.0001$), but were not significant in case of meropenem vs imipenem ($p\approx0.04$).

For Acinetobacter strains, the differences in MIC values distribution were not

Table 5. Compilation of MIC values for pairs of tested carbapenems on Pseudomonasspp. and Acinetobacter baumanni strains

| | DOR (1) *vs* IMP (2) | | | DOR (1) *vs* MER (2) | | | IMP (1) *vs* MER (2) | | |
|---|---|---|---|---|---|---|---|---|---|
| | $MIC_1 < MIC_2$ | $MIC_1 = MIC_2$ | $MIC_1 > MIC_2$ | $MIC_1 < MIC_2$ | $MIC_1 = MIC_2$ | $MIC_1 > MIC_2$ | $MIC_1 < MIC_2$ | $MIC_1 = MIC_2$ | $MIC_1 > MIC_2$ |
| *Pseudomonas* spp. (n = 42) | 95,2% (n = 40) | 4,8% (n = 2) | 0% (n = 0) | 85,7% (n = 36) | 4,8% (n = 2) | 9,5% (n = 4) | 4,8% (n = 2) | 19,0% (n = 8) | 76,2% (n = 32) |
| *Acinetobacter baumannii* (n = 16) | 31,2% (n = 5) | 50% (n = 8) | 18,8% (n = 3) | 50% (n = 8) | 37,8% (n = 6) | 12,5% (n = 2) | 31,2% (n = 5) | 43,9% (n = 7) | 25% (n = 4) |

statistically significant for any drug pair ($p>0.05$).

In case of Enterobacteriaceae strains, the differences in MIC values distribution were significant for almost all antibiotic pairs irrespective of ESBL – the only exception was doripenem vs meropenem, where $p\approx0.03$.

## DISCUSSION

Results of COMPACT have fully analyzed and published recently (1). Our results are not significantly different from these by Nordmann et al. (1). The only important difference was that our carbapenem$MIC_{90}$ values were paradoxically higher in strains collected from non-ICU. This can be explained simply by a small number of isolates. Another possible explanation is connected with the fact that the strains in our study were often collected from patients with chronic recurrent soft tissue and skin infections treated numerous times using various antimicrobial drugs, which favoured selection of multiresistant strains–unfortunately in Poland there are problems with selection of correct treatment regimens of such infections.

Our results may be related to these of Mendes et al. (2). In that study authors checked the sensitivity to doripenem of 36 614 hospital isolates of Enterobacteriaceae (including ESBL and AmpC strains) collected in the years 2000–2007 in the whole world. They showed that the $MIC_{90}$ value did not exceed 0.5 µg⁄ml for any of the tested species, which is consistent with the COMPACT study results (including our results). In the Mendes et al. study $MIC_{90}$ equal to 0.5 µg⁄ml referred to Morganellamorgani, for other species it was 0.06 or 0.12 µg⁄ml (similarly as for Enterobacteriaceae in the COMPACT study) (2). Results of Kaniga et al. appear interesting in this context (3). They showed higher $MIC_{90}$ values than us in 1830 Enterobacteriaceae strains collected during clinical studies on doripenem. It is worth remembering that the patients recruited to that study were patients with more severe infections, which may have been a factor that increased the MIC values.

A complex situation develops when comparing our results to data available in the literature on sensitivity of Pseudomonas spp. and Acinetobacter spp. to doripenem (4-8). In case of Pseudomonas spp. our results which show that the activity of doripenem exceeds that of imipenem and meropenem, are consistent with literature; it's different in case of Acinetobacter spp. According to European data, doripenem is the most active carbapenem, slightly more active that imipenem and definitely more active than meropenem; in the USA this order is different: imipenem is the most active, meropenem has intermediate and doripenem shows the lowest activity. Our results correlate to European data.

Our results show that with such refined methods of statistical analysis, we may demonstrate that there is a statistical significance of distribution of MIC values for each of the studied antimicrobial agents. It is important since the knowledge of MIC and specific pharmacokinetic data it may be decided whether the given drug dosage fulfils the pharmacodynamic requirements. Owing to the fact that MIC values of doripenem are usually lower than of other carbapenems, these requirements are easier to be met using lower doses, which is vital for patients in severe general status.

Koomanachai et al. published an interesting article, which showed the probability of meeting the pharmacodynamic requirements using mathematic modelling based on MIC values and Monte Carlo simulation of pharmacokinetic data in patients with normal renal function (9). As successful they considered the dosage regimen which achieved the probability of meeting these requirements in $\geq 90\%$. In case of A. baumannii it was not possible to achieve this goal for any of the drugs, in case of P. aeruginosa it was only possible for high doses of doripenem, cefepime, ceftazidime and meropenem administered as continuous infusion. Unfortunately such mode of administration of meropenem is very difficult because of the instability of the drug, which was demonstrated by Berthoin et al. (10). Therefore the only carbapenem, which may be administered in an optimal way (continuous infusion) in practice is doripenem. Latest literature data also support the use of doripenem in such way (11, 12, 13). The only difficulty here is such mode of administration in patients in good general status, which is not so important in case of ICU patients.

## CONCLUSIONS

1. Owing to low MIC values, doripenem may be an excellent choice in the treatment of infections caused by multiresistant Gram-negative bacteria.
2. Its beneficial pharmacologic properties (stability of infusion fluid) allow for optimal administration, as the only carbapenem, in continuous infusion.
3. In countries (such as Poland), where treatment of chronic and recurrent skin and subcutaneous tissue infections is far from ideal, it is crucial to modify the regimens and make them similar to countries where such treatment is optimal, otherwise there is always a risk of selection and spread of multiresistant Gram-negative strains.

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