Correlation between the Consumption of Meropenem or Doripenem and Meropenem Susceptibility of Pseudomonas aeruginosa in a University Hospital in Japan

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The appropriate use of carbapenems is essential in order to prevent resistance in Pseudomonas aeruginosa. We investigated the correlation between the consumption of meropenem or doripenem and the susceptibility of P. aeruginosa to meropenem in a Japanese university hospital from 2004 to 2009. The susceptibility data of P. aeruginosa and the annual consumption of meropenem or doripenem were analyzed. The consumption of meropenem or doripenem was calculated using the Anatomic Therapeutic Chemical classification and defined daily doses methodology. Meropenem consumption decreased and doripenem consumption increased and throughout the entire investigation period, total consumption of meropenem plus doripenem was stable. Although the annual number of isolated P. aeruginosa has not changed, the annual number of isolated multidrug-resistant P. aeruginosa decreased by measures against nosocomial infection. The rate of meropenem-resistant P. aeruginosa decreased in a time-dependent manner. Meropenem consumption was positively correlated with the meropenem resistance rate among P. aeruginosa (r=0.9455, p<0.01). The total consumption of meropenem and doripenem was not correlated with the meropenem resistance rate (r=-0.6601, p>0.1). These results suggested that even if the total consumption of meropenem plus doripenem was not changed, meropenem susceptibility among P. aeruginosa improved by the decrease of meropenem consumption. Although meropenem and doripenem have been suggested to show cross-resistance with each other, the reduction of meropenem consumption might be effective for preventing an increase of meropenem-resistant P. aeruginosa.

Key words meropenem; doripenem; Pseudomonas aeruginosa; susceptibility; consumption

Pseudomonas (P.) aeruginosa is an important nosocomial pathogen because it can cause complicated infections in immunodeficient patients and in compromised patients who have lost their ability to defend against infection. P. aeruginosa has developed resistance to its treatment by many antimicrobials. Carbapenems are recognized as one of the most effective antimicrobial agents against P. aeruginosa, and they tend to be used extensively for the treatment of P. aeruginosa infections in Japan. Previous studies have described that the increased use of carbapenems is associated with the emergence of carbapenem-resistant P. aeruginosa. Therefore, the appropriate use of carbapenems is essential in order to prevent an increase in the rate of resistance in P. aeruginosa. There are several reports about the relationship between carbapenem consumption and carbapenem susceptibility among P. aeruginosa; however, the results of these reports have been inconsistent, perhaps due to difference in antimicrobial susceptibility profile and antimicrobial prescribing practices in each country.

Although imipenem-, panipenem-, and biapenem-resistance are affected by the loss or reduction of the outer membrane porin protein OprD for influx, meropenem- and doripenem-resistance are derived by both the loss of OprD for influx and an increased expression of MexAB-OprM for efflux. Therefore, doripenem is believed to resemble meropenem in its antimicrobial activity and behavior. However, there is little information about the relationship between the consumption of meropenem or doripenem and meropenem susceptibility of P. aeruginosa.

In this study, we examined the annual change in the consumption of meropenem or doripenem and the rate of meropenem-resistant P. aeruginosa. Furthermore, we investigated the correlation between the consumption of meropenem or doripenem and the rate of meropenem-resistant P. aeruginosa in a university hospital in Japan.

MATERIALS AND METHODS

Antimicrobial Use Density of Each Carbapenem This study was conducted at Osaka University Hospital, which is a 1076-bed, teaching and academic hospital that provides tertiary and advanced medical care in Japan. We used an electronic record and ordering system, and all prescriptions of carbapenems in individual patients were monitored by the pharmacist using a computer system. Infectious disease physicians and pharmacists have utilized the prescription information for infection-control intervention, for example, dose adjustment and de-escalation. No other restrictive control measures on antimicrobial use have been implemented. Physicians can prescribe any antimicrobial in the formulary without restriction. We obtained the amount of all antimicrobial injections from the medical information database of the electronic health record system. These amounts were examined based on prescribed doses between January 2004 and December 2009. The amount of an antimicrobial agent was expressed as defined daily dose (DDD) and antimicrobial use density (AUD). The DDD is defined by the World Health Organization as the assumed mean maintenance adult daily dose of an antimicrobial agent for

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one day of treatment (anatomical therapeutic chemical classification/DDD index 2010).11) For carbapenems, DDD was as follows: meropenem, 2 g; doripenem, 1.5 g; imipenem, 2 g; panipenem, 2 g; and biapenem, 2 g. The AUD was expressed as DDD per 1000 patient-days for individual antimicrobial agents. We calculated patient-days by subtracting the day of admission from the day of discharge. Therefore, day cases scored zero patient-days.

**Meropenem Susceptibility among Pseudomonas aeruginosa** Culture and susceptibility data of 2777 P. aeruginosa strains that were isolated from hospitalized patients from January 2004 to December 2009 were evaluated. When multiple strains were isolated from the same site and from one patient within 1 month, they were regarded as the belonging to the same strain. Minimum inhibitory concentrations (MIC) were calculated by broth microdilution with the use of a Microscan system (Siemens Japan K.K., Tokyo, Japan). Antibiotic-resistant pathogens were determined by following the guidelines from the Clinical and Laboratory Standards Institute (CLSI). If the MIC was >4 mg/L, the P. aeruginosa isolate was considered non-susceptible to meropenem or imipenem. We defined multidrug resistant (MDR) P. aeruginosa as meeting the entire following MIC: ≥4 mg/L for ciprofloxacin, ≥16 mg/L for imipenem and ≥32 mg/L for amikacin.

**Statistical Analysis** Data were entered and analyzed with JMP 8.0.2 (SAS Institute, Inc., Cary, NC, U.S.A.). Linear regression analyses were used to measure the curve trend, and Pearson’s correlation coefficients (r) were used to assess the relationship between carbapenem consumption and the resistance rate of P. aeruginosa. p values less than 0.05 were regarded as significant in all analyses.

**RESULTS**

Figure 1 shows the change in the consumption of each carbapenem. The consumption of imipenem and panipenem decreased (AUD: from 4.81 to 1.49 and from 2.97 to 0.50, respectively). Biapenem consumption was not changed. Meropenem consumption, which was the highest of all carbapenems, decreased year by year (AUD: from 8.75 to 6.40). Doripenem was introduced as antibiotic therapy in Osaka University Hospital in December 1, 2005, its consumption increased significantly (AUD: from 0.76 to 2.73). A significant decrease in the total consumption of carbapenems was found between 2004 and 2009 (AUD, 17.45 and 12.36, respectively). The total consumption of meropenem plus doripenem was not changed during the entire investigation period. Although the annual number of P. aeruginosa isolated from patients has not changed, the annual number of MDR P. aeruginosa was markedly decreased (Table 1). The rate of imipenem- and meropenem-resistant P. aeruginosa decreased in a time-dependent manner.

Figure 2 shows the relationship between carbapenem consumption and the rate of meropenem-resistant P. aeruginosa in our university hospital in Japan. The rate of

**Table 1. Trend in Insusceptibility to Imipenem or Meropenem of Pseudomonas aeruginosa Isolated from Inpatients between 2004 and 2009**

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of P. aeruginosa</td>
<td>480</td>
<td>455</td>
<td>447</td>
<td>488</td>
<td>439</td>
<td>468</td>
</tr>
<tr>
<td>No. of MDR P. aeruginosa</td>
<td>20</td>
<td>16</td>
<td>8</td>
<td>15</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Imipenem</td>
<td>26</td>
<td>24</td>
<td>17</td>
<td>15</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Meropenem</td>
<td>17</td>
<td>17</td>
<td>15</td>
<td>12</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

MDR, multidrug resistant.
meropenem-resistant *P. aeruginosa* 17% between 2004 and 2005, and the rate markedly decreased to 6% in 2009. The rate of meropenem-resistant *P. aeruginosa* decreased in a time-dependent manner, and it showed a significant positive correlation with the decrease of meropenem consumption \((r = 0.9455, p < 0.01)\). However, the total consumption of meropenem plus doripenem was not correlated with the rate of meropenem-resistant *P. aeruginosa\((r = -0.6601, p > 0.1)\).

**DISCUSSION**

This study evaluated the relationship between carbapenem consumption and the carbapenem resistance of *P. aeruginosa* in a university hospital in Japan. In our hospital, we have implemented the monitoring of the usage of antimicrobials and the infection-control intervention such as dose adjustment and de-escalation. The antimicrobial therapy based on pharmacokinetics-pharmacodynamics theory is performed progressively, and the administration period of carbapenems became shorter by this action.\(^{12}\) Although there was no significant change in the annual number of isolated *P. aeruginosa*, the annual number of MDR *P. aeruginosa* was markedly decreased by the measures against nosocomial infection. In this study, the total consumption of meropenem was correlated with the rate of meropenem-resistant *P. aeruginosa*. Therefore, we think that the decrease of meropenem consumption is efficient for increase of meropenem susceptibility among *P. aeruginosa*. However it is an undeniable fact that the shortening of administration period and the increase of consumption of hand disinfectants influenced the detection of drug-resistant bacteria.\(^{13–15}\)

Previous reports have described that the consumption of each carbapenem was not correlated with the carbapenem resistance rate of *P. aeruginosa*.\(^{16–18}\) Shigemi et al. reported that there was a significant correlation between the total AUD of meropenem plus doripenem and meropenem susceptibility among *P. aeruginosa*, but there was no correlation between the AUD of meropenem alone and meropenem susceptibility.\(^{19}\) The consumption of meropenem and doripenem were increased in their studies.

Similar mechanisms have been reported for doripenem, as with meropenem, for antimicrobial activity and behavior.\(^{10}\) But recent reports have suggested that the isolation frequencies of carbapenem-resistant mutants were lower with doripenem than with meropenem.\(^{19,20}\) We think that a low mutation frequency in carbapenem resistance by doripenem and the decrease of meropenem consumption affected the improvement of meropenem susceptibility among *P. aeruginosa*. Credito et al. reported that, although the MIC of meropenem among *P. aeruginosa* was similar to the MIC of doripenem, the mutant prevention concentration (MPC) of meropenem was 2 times higher than that of doripenem.\(^{21}\) The difference in the MPC/MIC ratio between meropenem and doripenem may have affected the findings of the present study. Although it has been suggested that meropenem and doripenem show cross-resistance with each other, these results suggest that changing from meropenem to doripenem has a possibility to improve meropenem susceptibility among *P. aeruginosa* in contrast to the report from Shigemi et al.\(^{21}\) The main reasons for resistance of *P. aeruginosa* were a loss of OprD activity and increased expression of MexAB-OprM rather than metallo-beta-lactamase, because only a few carbapenem-resistant strains produce metallo-beta-lactamase.\(^{22}\) We think that the fewer isolation frequency of metallo-beta-lactamase producing *P. aeruginosa* might influence the result.

In conclusion, although doripenem consumption increased, meropenem susceptibility among *P. aeruginosa* was improved by the decrease of meropenem consumption. Although meropenem and doripenem have been suggested to show cross-resistance with each other because they have similar antimicrobial activity and behavioral mechanisms, the reduction of meropenem consumption by switching from meropenem to other carbapenem, including doripenem, might be effective for preventing an increase of meropenem-resistant *P. aeruginosa*. But we think that excessive use of one carbapenem encourages the emergence of carbapenem-resistant *P. aeruginosa*. The appropriate use of carbapenems is important to prevent the development of carbapenem-resistant strain.

**REFERENCES**


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