Postantibiotic Effect of Carbapenems against Pseudomonas aeruginosa

MUNEO HIKIDA*, YOSHIIKIYAMAZAKI, MASHUHITOYOSHIDA, KOUSUKEKAWASHIMA, KATSUMUKISHIKI and SUSUMUMITSUSHI†

Biological Research Laboratories, Lederle (Japan), Ltd., 1-6-34, Kashiwa-cho, Shiki-ishi, Saitama 353, Japan

†Episome Institute, 2220 Kogure, Fujimi-mura, Setagun, Gunma 371-01, Japan

(Received for publication April 12, 1995)

Recently, nontraditional β-lactam antibiotics, carbapenems, have been synthesized vigorously, and several analogs are under development. With respect to the antimicrobial activity of carbapenems, the postantibiotic effect (PAE) is a prominent feature. Carbapenems have been shown to produce PAEs not only against Gram-positive bacteria but also against Gram-negative bacteria by several investigators1 ~ 5). The aim of the present study was to simultaneously compare the PAE of newer carbapenems (such as meropenem and biapenem) with that of imipenem against strain NU12 of Pseudomonas aeruginosa.

Biapenem and meropenem were synthesized at Chemical and Formulation Laboratories of Lederle (Japan), Ltd. All other antibiotics were obtained from commercial sources.

MICs were determined by the two-fold agar dilution method.

Culture was grown in Sensitivity Test Broth (STB; Nissui Pharmaceutical, Japan) or on Sensitivity Disk Agar-N (SDA; Nissui).

The in vitro PAE of each antibiotic was studied using P. aeruginosa NU12 in the logarithmic phase of growth (10^6 cfu/ml), which had been exposed to 4 x MIC of the respective antibiotic at 37°C for 2 hours. The antibiotic was removed by a 10^-2 dilution into fresh STB medium, and then the culture was reincubated at 37°C in a shaking water bath. Thereafter, viable count was determined every 1 hour by inoculating a series of dilutions of a bacterial suspension onto the SDA plates.

Plasma concentrations of the parent compound in mice given a dose of 50 mg/kg were determined by HPLC assay, and the optimal fitting curve of time courses of the concentrations was obtained based upon a one-compartment model to calculate the “time above MIC” value.

As shown in Table 1, the MICs of imipenem/cilastatin, meropenem, biapenem and ceftazidime for P. aeruginosa NU12 used in this study were 3.13, 3.13, 1.56 and 3.13 μg/ml, respectively. The time-above-MIC (hour) values determined by pharmacokinetic studies are also shown in Table 1. It is well-known that the PAE values obtained are very variable possibly because of dependence upon methods used to quantify the effect. Therefore, we made a simultaneous comparison among the PAE values of various carbapenems using a single method. The in vitro PAE values of imipenem/cilastatin, meropenem, biapenem and ceftazidime obtained from the standard viable counting method were 1.8, 1.5, 1.6 and -1.0 hours, respectively (Fig. 1, Table 1: Table 1 shows the in vitro PAE calculated from Fig. 1). The in vivo PAE evaluated in the neutropenic mouse thigh model gave results as follows: imipenem/cilastatin 0.9, meropenem 1.5, biapenem 1.8 and ceftazidime -0.5 hours (Fig. 2, Table 1: Table 1 shows the in vivo PAE calculated from Fig. 2).

PAE values mentioned above represent mean values from two experiments. Both in vitro and in vivo PAE values obtained in this study were very similar to the results reported by other investigators5,6,7). As shown

Table 1. Postantibiotic effect of carbapenems against Pseudomonas aeruginosa NU12 in vitro and in vivo.

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC (μg/ml)</th>
<th>4xMIC (μg/ml)</th>
<th>PAE* (hour)</th>
<th>Dose (mg/kg)</th>
<th>Time above MIC (hour)</th>
<th>PAE* (hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>imipenem/cilastatin</td>
<td>3.13</td>
<td>12.5</td>
<td>1.8</td>
<td>50</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>meropenem</td>
<td>3.13</td>
<td>12.5</td>
<td>1.5</td>
<td>50</td>
<td>0.86</td>
<td>1.5</td>
</tr>
<tr>
<td>biapenem</td>
<td>1.56</td>
<td>6.25</td>
<td>1.6</td>
<td>50</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>3.13</td>
<td>12.5</td>
<td>-1.0</td>
<td>50</td>
<td>2.0</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

*PAE, postantibiotic effect.
Fig. 1. *In vitro* postantibiotic effect of imipenem/cilastatin, meropenem, biapenem and ceftazidime against *Pseudomonas aeruginosa* NU12.

- Imipenem/cilastatin, □ meropenem, △ biapenem, ◯ ceftazidime, ● control.

Table 1, the time-above-MIC values for antibiotics tested ranged from 0.86 to 2.0 hours. With respect to the biochemical basis of the PAE, Gould et al. expressed the notion that affinity for PBP2 relates to induction of PAE. Several other theories have been proposed, but not been conclusively elucidated. Thus, this study showed that all carbapenems tested induced a PAE against *P. aeruginosa* NU12, whereas ceftazidime caused no PAE. The fact that carbapenems, unusually for a β-lactam antibiotic, produce a PAE against a strain NU12 of *P. aeruginosa* will spur further research and development of new carbapenem derivatives.

References


