Effects of Cilastatin on the Pharmacokinetics of a New Carbapenem, DA-1131, in Rats, Rabbits, and Dogs

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DA-1131, a new carbapenem antibiotic, undergoes renal metabolism by renal dehydropeptidase I (DHP-I), located on the brush border of the proximal tubular cell. Species differences with regard to the effects of cilastatin, a renal DHP-I inhibitor, were investigated after a 1-min intravenous infusion of DA-1131, with or without cilastatin, to rats, rabbits, and dogs. After intravenous infusion, the nonrenal clearance (CL\textsubscript{NR}) of DA-1131 was significantly slower in rats (3.00 versus 8.01 ml/min/kg) and rabbits (2.41 versus 6.77 ml/min/kg) when the drug was coadministered with cilastatin; this could be due to the slower metabolism of DA-1131 by rat and rabbit kidney DHP-I. This indicated that renal metabolism of DA-1131 by renal DHP-I was inhibited by cilastatin. However, coadministration with cilastatin to dogs did not affect the CL\textsubscript{NR} of DA-1131.

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was collected over an 8-h period. Other procedures were similar to previously reported methods (15).

DA-1131 (treatment V) or DA-1131–cilastatin (1:1 ratio [23]; treatment VI), at 50 mg of DA-1131/kg, was administered intravenously to male dogs (n = 6) over a 1-min period via the cephalic vein (the total injection volume was approximately 10 ml) by parallel design. Approximately 2.5-ml volumes of blood were collected via the other cephalic vein at 0 (to serve as a control), 1 (at the end of the infusion), 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, and 480 min after intravenous administration of the drug. Urine was collected over an 8-h period. Other procedures were similar to those reported previously (21). The DA-1131 in the biological samples described above was analyzed within 7 days by the previously reported high-performance liquid chromatographic method developed by our laboratory (18).

Standard methods (6) were used to calculate the following pharmacokinetic parameters: the total area under the plasma concentration-time curve from time zero to infinity (AUC0–∞) (1), the time-averaged total body clearance (CL), the area under the first moment of the plasma concentration-time curve (AUMC0–∞), the mean residence time (MRT), the apparent volume of distribution at steady state (Vss), and the terminal half-life (τ) (5) were calculated by the harmonic mean method.

Levels of statistical significance were assessed by the t test between two means for unpaired (rat and rabbit studies) and paired (dog study) data. Significant differences were judged as a P value of less than 0.05. All results are expressed as means ± standard deviations.

The mean arterial plasma concentration-time profiles of DA-1131 in rats (treatments I and II) are shown in Fig. 1A, and some relevant pharmacokinetic parameters are listed in Table 1. After intravenous administration of the drug to rats, the plasma concentrations of DA-1131 declined in a polyexponential fashion for both treatment groups and were significantly higher for treatment II than for treatment I (Fig. 1A). The significantly higher plasma concentrations (Fig. 1A) and the significantly greater AUC0–∞ (32% increase) of DA-1131 in rats when given in combination with cilastatin (treatment II) could be due to a significantly slower CL of DA-1131 (24% decrease) in treatment II (Table 1). The significantly slower CL in treatment II was due to a significantly slower CLNR (63% decrease) with this treatment, because the CLR values for the two rat groups were not significantly different (Table 1). The significantly slower CLNR in treatment II could be due to a considerably slower metabolism of DA-1131 by DHP-I in the rat kidney in the presence of cilastatin. The above data indicated that the metabolism of DA-1131 by rat renal DHP-I was inhibited by cilastatin. This was supported by a significant increase in the percentage of the intravenous dose of DA-1131 excreted in urine over an 8-h period as unchanged drug (56% increase) in treatment II (Table 1). The CLR values for the two treatments were not significantly different (Table 1), indicating that the CLR of DA-1131 was not affected by cilastatin. The Vss of DA-1131 was significantly larger (32% increase) in treatment II. The exact reason for this is not clear; however, it was not due to an increase in the unbound fraction of DA-1131 in plasma due to cilastatin, since the level of plasma protein binding of DA-1131 in the rat was less than 10% (17). The significantly slower CL and significantly larger Vss of DA-1131 in treatment II resulted in a significantly longer terminal t1/2 and MRT (Table 1).

The mean arterial plasma concentration-time profiles of DA-1131 in rabbits (treatments III and IV) are shown in Fig. 1B, and, again, some relevant pharmacokinetic parameters are listed in Table 1. After intravenous administration of the drug to rabbits, the plasma concentrations of DA-1131 declined in a polyexponential fashion for both treatment groups and were significantly higher in treatment IV than in treatment III (Fig. 1B). The significantly higher plasma concentrations (Fig. 1B) and the significantly greater AUC0–∞ (160% increase) for DA-1131 when given in combination with cilastatin (treatment IV) to rabbits could be due to a significantly slower CL of DA-1131 (62% decrease) in treatment IV (Table 1). The significantly slower CL in treatment IV was due to a significantly slower CLR (67% decrease) and CLNR (64% decrease) in treatment IV (Table 1). In the previous rabbit studies (15, 17), it was found that DA-1131 was excreted in urine via glomerular filtration and active secretion. The CLR of DA-1131 was signif-

![Figure 1](http://aac.asm.org/)
Table 1. Pharmacokinetic parameters of DA-1131

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Pharmacokinetic parameter</th>
<th>CL (ml/min/kg)</th>
<th>CL (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbits</td>
<td>AUC_{0–t} (mg/kg)</td>
<td>15.2 ± 3.5</td>
<td>15.9 ± 2.4</td>
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<td></td>
<td>Vss (ml/kg)</td>
<td>12.9 ± 2.1</td>
<td>18.2 ± 1.5</td>
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<tr>
<td></td>
<td>CL (ml/min/kg)</td>
<td>12.0 ± 1.7</td>
<td>20.3 ± 1.4</td>
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<tr>
<td></td>
<td>Vm (min)</td>
<td>6.8 ± 1.2</td>
<td>10.8 ± 1.6</td>
</tr>
<tr>
<td></td>
<td>m (min/ml)</td>
<td>10.5 ± 2.1</td>
<td>16.0 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>T_{1/2}</td>
<td>15.2 ± 4.6</td>
<td>19.1 ± 3.5</td>
</tr>
<tr>
<td>Treatment I</td>
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<td>7.5 ± 1.7</td>
<td>12.8 ± 2.4</td>
</tr>
<tr>
<td>Treatment II</td>
<td></td>
<td>6.2 ± 1.2</td>
<td>9.1 ± 1.8</td>
</tr>
<tr>
<td>Rabbits</td>
<td></td>
<td>10.0 ± 1.6</td>
<td>14.0 ± 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.5 ± 1.3</td>
<td>10.2 ± 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15.2 ± 3.5</td>
<td>19.1 ± 3.5</td>
</tr>
<tr>
<td>Treatment III</td>
<td></td>
<td>6.8 ± 1.2</td>
<td>10.8 ± 1.6</td>
</tr>
<tr>
<td>Treatment IV</td>
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<td>10.5 ± 2.1</td>
<td>16.0 ± 2.4</td>
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<tr>
<td>Treatment V</td>
<td></td>
<td>15.2 ± 4.6</td>
<td>19.1 ± 3.5</td>
</tr>
<tr>
<td>Treatment VI</td>
<td></td>
<td>7.5 ± 1.7</td>
<td>12.8 ± 2.4</td>
</tr>
</tbody>
</table>

Values are means ± standard deviations.

In conclusion, species differences in the metabolism of DA-1131 by renal DHP-I were observed. Coadministration with cilastatin caused a significantly slower CL_{NR} of DA-1131 in rats by inhibition of renal DHP-I, and this resulted in a significant increase in urinary excretion of DA-1131 in these animals. Cilastatin also caused a significantly slower CL_{NR} of DA-1131 by inhibition of renal DHP-I and a significantly slower CLR by inhibition of the tubular secretion of DA-1131 in dogs. However, coadministration with cilastatin did not affect the CL_{NR} of DA-1131 in dogs. The above data suggested that the stability of DA-1131 to renal DHP-I varied widely in the three animal species studied.

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REFERENCES


