Pharmacokinetics of a New Carbapenem, DA-1131, after Intravenous Administration to Rats with Uranyl Nitrate-Induced Acute Renal Failure

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Because the physiological changes that occur in patients with acute renal failure could alter the pharmacokinetics of the drugs used to treat the disease, the pharmacokinetics of DA-1131, a new carbapenem antibiotic, were investigated after 1-min intravenous administration of the drug (50 mg/kg of body weight) to control rats and rats with uranyl nitrate-induced acute renal failure (U-ARF rats). The impaired kidney function was observed in U-ARF rats on the basis of physiological parameters observed by microscopy of the kidney and obtained by chemical analysis of the plasma. After a 1-min intravenous infusion of DA-1131, the concentrations in plasma and the total area under the plasma concentration-time curve from time zero to time infinity increased significantly in U-ARF rats compared with those in control rats (13,000 versus 4,400 μg·min/ml). This was due to the significantly slower total body clearance (CL) of DA-1131 (3.84 versus 11.4 ml/min/kg) from U-ARF rats than from control rats. The significantly slower CL of DA-1131 from U-ARF rats was due to both significantly slower renal clearance (0.006635 versus 4.95 ml/min/kg because of a significant decrease in the 8-h urinary excretion of unchanged DA-1131 [1.54 versus 43.8% of the intravenous dose] due to impaired kidney function, as proved by the significant decrease in creatinine clearance [0.0159 versus 4.29 ml/min/kg]) and significantly slower nonrenal clearance (3.80 versus 6.34 ml/min/kg because of a significant decrease in the metabolism of DA-1131 in the kidney) in U-ARF rats. The amounts of DA-1131 recovered from all tissues studied (except the kidneys) were significantly higher for U-ARF rats than for control rats; however, the ratios of the amount in tissue to the concentration in plasma (except those for the kidney, small intestine, and spleen) were not significantly different between the two groups of rats, indicating that the affinity of DA-1131 for rat tissues was not changed considerably in U-ARF rats.

Drugs are eliminated from the body by metabolism (mainly in the liver) and/or excretion (mainly via the kidney by glomerular filtration and/or renal tubular secretion). It has been reported that the total body clearance (CL) renal clearance (CLR) and/or nonrenal clearance (CLNR) of drugs which were eliminated mainly by metabolism and by excretion were altered in rats with uranyl nitrate-induced acute renal failure (U-ARF rats). The drugs eliminated mainly by metabolism include propranolol (22), theophylline (12), amiodarone (8), diltiazem (9, 20), nifedipine (1, 6, 10), and verapamil (11). A large number of drugs, including adriamycin (18), the drugs eliminated mainly by excretion include vancomycin (7) and methylprednisolone (20). Therefore, it could be expected that the pharmacokinetics and hence the pharmacodynamics of drugs could be altered in renal failure. It has been reported previously (17) that uranyl nitrate-induced acute renal failure causes both liver and kidney impairment in Sprague-Dawley rats on the basis of plasma chemistry data and tissue microscopy.

DA-1131, (1R,5S,6S)-(2S,4S)-2-[(E)-3-methansulfonylamino-1-propenyl]pyrrolidine-4-ylthio]-6-[(R)-1-hydroxyethyl]-1-methyl-1-carbapen-2-εm-3-carboxylic acid (Fig. 1), a new carbapenem antibiotic, has a broad spectrum of activity against both the gram-positive and gram-negative organisms (10). DA-1131 was resistant to degradation by various types of β-lactamas (4). DA-1131 was relatively stable against hydrolysis of ICR mouse, Sprague-Dawley rat, New Zealand White rabbit, beagle dog, and human renal dehydropeptidase I (DHP-I) compared with imipenem and meropenem (11). Judging from the Vmax/Km ratios, DA-1131 showed relatively greater resistance (compared with those of imipenem and meropenem) to mouse, rat, rabbit, dog, and human renal DHP-I; the ratios of DA-1131 for resistance to DHP-I were from 1.3 to 4.6 times greater than those of imipenem and meropenem (unpublished data). DA-1131 is now being evaluated in a preclinical study. DA-1131 was chosen as a model drug in the present study because approximately 50% of the intravenous dose was excreted via the kidneys in rats. Therefore, changes in both CLR and CLNR of the drug could be expected in U-ARF rats.

The purpose of this study was to investigate the effect of uranyl nitrate-induced acute renal failure on the pharmacokinetics and tissue distribution of DA-1131 after intravenous administration to control and U-ARF rats.

MATERIALS AND METHODS

Chemicals. DA-1131 (as the HCl salt) was donated by the Research Laboratories, Dong-A Pharmaceutical Company (Yongin, Korea). Uranyl nitrate was purchased from BDH Chemicals Ltd. (Poole, England). The other chemicals were of reagent grade or high-performance liquid chromatography (HPLC) grade and were used without further purification.

Animals. Male Sprague-Dawley rats (weight, 265 to 320 g) were purchased from Charles River Company (Atsugi, Japan). The rats were randomly divided into two groups, control and U-ARF rats.

Induction of acute renal failure in rats by uranyl nitrate injection. Uranyl nitrate (the powder was dissolved in injectable normal saline solution to make a concentration of 0.5%), 1 ml/kg of body weight (5 mg/g), was injected once via...
In 10% neutral phosphate-buffered formalin and were processed for routine excised, rinsed or perfused with injectable normal saline solution, blotted dry and stored at 70°C in a freezer (Revco ULT 1490 D-N-S) until HPLC analysis of DA-1131 (16). Plasma samples were also diluted with 4 volumes of distilled water. All the procedures were conducted at 4°C on an ice bath.

HPLC assay. The DA-1131 in the biological samples was analyzed within 7 days by the previously reported HPLC method developed by our laboratory (16). The mobile phase, 0.015 M KH2PO4-acetonitrile (9:1 [vol/vol]; pH 5.0), was run through a reversed-phase column at a flow rate of 0.6 ml/min, and the column effluent was monitored with a UV detector set at 300 nm. The retention time of DA-1131 was approximately 8.0 min. The detection limits of DA-1131 in human plasma and urine were 2.85% (range, 1.76 to 5.04%) and 2.85% (range, 1.65 to 4.75%), respectively. The mean between-day coefficients of variation for the analysis of the same samples on 3 consecutive days were 2.30 and 4.29% in human plasma and urine, respectively.

Measurement of total protein, albumin, urea nitrogen, and creatinine levels. Total protein, albumin, urea nitrogen, and creatinine levels in plasma and creatinine levels in urine were measured with an Hitachi 747 instrument (Hitachi, Tokyo, Japan).

Pharmacokinetic analysis. The total area under the plasma concentration-time curve (AUC) from time zero to time infinity (AUC0–∞) was calculated by the trapezoidal rule-extrapolation method (13); this method uses the logarithmic trapezoidal rule to calculate the area during the phase when the level in plasma is declining (1) and the linear trapezoidal rule for the phase when the level in plasma is rising. The area from the last datum point to infinity was estimated by dividing the last concentration measured in plasma by the terminal rate constant.

A standard method (9) was used to calculate the following pharmacokinetic parameters: the time-averaged 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), the time-averaged CLAUC and the time-averaged CLAUC (13).

The mean values of CL (L/min), Vss (ml), and terminal half-life (t½) (6) were calculated by the harmonic mean method.

Creatinine clearance (CLCR) was calculated by dividing the total amounts of creatinine excreted in urine over 8 h by the AUC from 0 to 8 h (AUC0–8) for creatinine (the concentration of creatinine in plasma was measured 8 h after administration of the intravenous dose), assuming that the kidney function was stable during the 8-h experimental period. The kidney function seemed to be stable since the CLCR for the control rats (4.29 ml/min/kg; see Table 1) was very similar to the values reported in the literature (3 to 5 ml/min/kg) and the impaired kidney function in U-ARF rats continued from the third day to the fifth day after a single injection of uranyl nitrate into the rats (12, 17).

Statistical analysis. Levels of statistical significance were assessed by the t test between two means for unpaired data. Significant differences were judged as a P value of less than 0.05. All results are expressed as means ± standard deviations.

RESULTS
Induction of acute renal failure in rats. In the U-ARF rats in the present study, the impaired kidney function was obvious; the levels of urea nitrogen in plasma (205 versus 17.1 mg/dl) and kidney weight (1.02 versus 0.803% of body weight) increased significantly and the CLCR value (0.0159 versus 4.29 ml/min/kg) decreased significantly compared with those for control rats (Table 1). Impaired kidney function in U-ARF rats was also supported by kidney microscopy; extensive tubular

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**TABLE 1. Values of physiological parameters for plasma and organ (liver and kidney) weight of control and U-ARF rats**

<table>
<thead>
<tr>
<th>Rat</th>
<th>Body wt (g)</th>
<th>Level in plasma</th>
<th>CLCR (mll/min/kg)</th>
<th>Organ wt (% of body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Urea nitrogen</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Control (n = 10)</td>
<td>286 ± 6.25</td>
<td>293 ± 8.15</td>
<td>17.1 ± 5.89</td>
<td>0.460 ± 0.0516</td>
</tr>
<tr>
<td>U-ARF (n = 13)</td>
<td>290 ± 8.53</td>
<td>278 ± 12.54</td>
<td>205 ± 34.22</td>
<td>4.62 ± 1.322</td>
</tr>
</tbody>
</table>

* Values are means ± standard deviations.
* Measured just before the administration of uranyl nitrate.
* Measured on the fifth day after a single administration of uranyl nitrate.
* P < 0.01.
* P < 0.001.
necrosis was present. Similar results have also been reported elsewhere (5, 7, 8, 12, 22). However, no significant findings were found by liver microscopy for both groups of rats and kidney microscopy for control rats. In U-ARF rats, the levels of albumin (2.37 versus 3.15 g/dl) and total protein (4.71 versus 5.48 g/dl) in plasma decreased significantly compared with those in control rats (Table 1). Note that body weight gain decreased significantly for rats pretreated with uranyl nitrate (from 290 to 278 g) (Table 1).

**Pharmacokinetics of DA-1131 after intravenous administration.** After intravenous administration of DA-1131 to control rats, the mean levels of DA-1131 in arterial plasma declined rapidly (Fig. 2), with a mean $t_{1/2}$ of 15.3 min (Table 2), and were detected only up to 2 h (Fig. 2) due to the sensitivity of our HPLC assay. However, in U-ARF rats they declined slowly (Fig. 2), with a mean $t_{1/2}$ of 61.5 min (Table 2), and were detected for up to 6 h (Fig. 2). The $t_{1/2}$ values were significantly different. The concentrations of DA-1131 in plasma were significantly higher in U-ARF rats than in control rats (Fig. 2), and this resulted in a significant increase in the AUC$_{0-\infty}$ (13,000 versus 4,400 μg · min/ml) and the AUMC$_{0-\infty}$ (948,000 versus 49,600 μg · min²/ml) for DA-1131 in U-ARF rats (Table 2). The CL (3.84 versus 11.4 ml/min/kg), CL$_R$ (0.000635 versus 4.95 ml/min/kg), and CL$_{NR}$ (3.80 versus 6.34 ml/min/kg) of DA-1131 were significantly slower in U-ARF rats (Table 2). The $V_{SS}$ of DA-1131 increased significantly in U-ARF rats (259 versus 124 ml/kg) (Table 2).

**Distribution of DA-1131 in tissue after intravenous administration.** The mean amounts of DA-1131 recovered from all tissues studied except kidney were significantly higher in U-ARF rats than in control rats (Table 3). However, the ratios of the amount in tissue to the concentration in plasma (T/P ratios) for each tissue studied except the kidney, small intestine,
and CLNR (3.80 versus 6.34 ml/min/kg) of DA-1131 in U-ARF rats resulted in a significant increase in the CLNR of DA-1131 in U-ARF rats could be due to the considerable slower CL, CLR, and/or CL NR after intravenous administration of vancomycin (7), amiodarone (8), diltiazem (19), azosemide (21), methotrexate (20), and DA-125 (17) to U-ARF rats. Significant decreases in the values of amounts of unchanged DA-1131 excreted in urine over 8 h was excreted as unchanged drug in bile over 8 h after the appearance (mainly due to metabolism) on the basis of an in vitro bacterial l-lactamases, abstr. p. 237.

The significant increase in the AUC 0–8) compared with the amounts excreted unchanged from DA-1131 (3.84 versus 11.4 ml/min/kg) in U-ARF rats (Table 2). The impaired kidney function of DA-1131 (0.000635 versus 4.95 ml/min/kg) in U-ARF rats (Table 2). The significant slower CL R of DA-1131 in U-ARF rats was due to the significantly slower CL.

because the level of plasma protein binding of DA-1131 was considerably low in U-ARF rats (approximately 10% in Sprague-Dawley rat plasma) (15).

DA-1131 was highly concentrated in the kidneys of the control rats (39.2 µg per g of tissue), as reflected by the greater-than-unity value of the T/P ratio (2.00) for the organ. This was expected because the kidney was the main organ excreting unchanged DA-1131 in rats (43.8% of the intravenous dose of DA-1131) (Table 2). The T/P ratios of DA-1131 for all rat tissues studied (except the kidneys) were less than unity for control rats; however, the T/P ratios were not significantly different between the two groups of rats except for the kidneys, small intestine, and spleen (Table 3). These data indicate that the affinity of DA-1131 for rat tissues is not affected considerably by acute renal failure.

ACKNOWLEDGMENTS

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REFERENCES


and spleen were not significantly different between control and U-ARF rats.

DISCUSSION

The significant increase in the AUCt and AUMCt of DA-1131 in U-ARF rats was due to the significantly slower CL of DA-1131 (3.84 versus 11.4 ml/min/kg) in U-ARF rats (Table 2). The significantly slower CL in U-ARF rats was due to the significantly slower both CLR (0.000635 versus 4.95 ml/min/kg) and CLNR (3.80 versus 6.34 ml/min/kg) of DA-1131 in U-ARF rats (Table 2). The significantly slower CLR of DA-1131 in U-ARF rats could be due to the impaired kidney function; the CLR value was significantly reduced (0.0159 versus 4.29 ml/ min/kg) in U-ARF rats (Table 2). The impaired kidney function in U-ARF rats resulted in a significant decrease in the amounts of unchanged DA-1131 excreted in urine over 8 h (AUCt) compared with the amounts excreted unchanged from control rats (1.54 versus 43.8%) (Table 2). Similar results were also reported for DA-125 (17), adriamycin (18), methotrexate (20), and azosemide (21). Significant decreases in the values of CLt, CLR, and/or CLNR after intravenous administration of vancomycin (7), amiodarone (8), diltiazem (19), azosemide (21), methotrexate (20), and DA-125 (17) to U-ARF rats have also been reported. The contribution of biliary excretion of unchanged DA-1131 to the CLNR of DA-1131 after intravenous administration of the drug to rats seemed to be minor, because less than 1.76% of the intravenous dose of DA-1131 was excreted as unchanged drug in bile over 8 h after the intravenous administration of DA-1131 at 200 mg/kg to four to six rats (15). Therefore, the CLNR of DA-1131 could represent the metabolic clearance of DA-1131. The significantly slower CLNR of DA-1131 in U-ARF rats could be due to the considerably slower metabolism of DA-1131 in rat kidney because rat kidney was one of the main organs into which DA-1131 disappeared (mainly due to metabolism) on the basis of an in vitro tissue homogenate study with Sprague-Dawley rats (15).

The significant increase in the VSS of DA-1131 in U-ARF rats resulted in a significant increase in the t1/2 (61.5 versus 15.3 min) and the MRT (71.0 versus 11.2 min) of DA-1131 in U-ARF rats (Table 2). This was not mainly due to the increase in the unbound fraction of DA-1131 in U-ARF rat plasma

### TABLE 3. Amount of DA-1131 recovered from 30 min after a 1-min intravenous infusion of the drug (50 mg/kg) to control and U-ARF rats

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Amt (µg/ml of plasma or µg/g of tissue) recovered</th>
<th>Ratioa</th>
<th>Control rats (n = 7)</th>
<th>U-ARF rats (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>19.8 ± 3.55</td>
<td>116 ± 8.30</td>
<td>5.86</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>1.25 ± 0.335 (0.0637 ± 0.0135)c</td>
<td>3.82 ± 1.06 (0.0620 ± 0.0793)</td>
<td>3.06</td>
<td></td>
</tr>
<tr>
<td>Fat</td>
<td>1.68 ± 0.685 (0.0844 ± 0.0288)</td>
<td>16.7 ± 8.31 (0.143 ± 0.0697)</td>
<td>9.94</td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td>3.17 ± 0.785 (0.161 ± 0.0266)</td>
<td>14.9 ± 6.13 (0.128 ± 0.0499)</td>
<td>4.70</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>39.2 ± 7.92 (2.00 ± 0.279)</td>
<td>10.5 ± 2.36 (0.0909 ± 0.0204)c</td>
<td>0.208</td>
<td></td>
</tr>
<tr>
<td>Large intestine</td>
<td>2.67 ± 0.623 (0.140 ± 0.0486)</td>
<td>13.7 ± 3.79 (0.117 ± 0.0246)</td>
<td>5.13</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>7.84 ± 1.22 (0.402 ± 0.0568)</td>
<td>44.7 ± 18.8 (0.387 ± 0.167)</td>
<td>5.70</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>3.58 ± 3.84 (0.185 ± 0.200)</td>
<td>17.5 ± 5.74 (0.152 ± 0.0402)</td>
<td>4.89</td>
<td></td>
</tr>
<tr>
<td>Mesentery</td>
<td>3.76 ± 1.18 (0.189 ± 0.0376)</td>
<td>23.3 ± 5.73 (0.199 ± 0.0359)</td>
<td>6.20</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>2.09 ± 0.471 (0.107 ± 0.0206)</td>
<td>12.7 ± 3.56 (0.109 ± 0.0245)</td>
<td>6.08</td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>9.91 ± 3.65 (0.546 ± 0.351)</td>
<td>24.2 ± 9.16 (0.210 ± 0.0850)c</td>
<td>2.44</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>1.07 ± 0.478 (0.0542 ± 0.0206)</td>
<td>11.2 ± 2.40 (0.0961 ± 0.0144)c</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>3.50 ± 0.846 (0.178 ± 0.0366)</td>
<td>23.7 ± 6.38 (0.205 ± 0.0460)</td>
<td>6.77</td>
<td></td>
</tr>
</tbody>
</table>

a Values are means ± standard deviations.
b Ratio of amount for U-ARF rats to amount for control rats.
c P < 0.001.
d Numbers in parentheses are the mean ± standard deviation T/P ratios.
e P < 0.01.
f P < 0.05.


