Steady-State Pharmacokinetics of Intramuscular Imipenem-Cilastatin in Elderly Patients with Various Degrees of Renal Function

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We studied the concentrations in plasma and pharmacokinetics of imipenem and cilastatin in elderly patients (greater than 65 years old) who had various degrees of renal function and who were hospitalized with soft tissue infections. Three groups of patients received imipenem-cilastatin (500/500 mg) intramuscularly every 12 h: group I consisted of eight patients with a creatinine clearance (\(CL_{\text{CR}}\)) of >50 ml/min (range, 51 to 84 ml/min; mean, 65.8 ml/min); group II consisted of three patients with a \(CL_{\text{CR}}\) of 20 to 50 ml/min; and group III consisted of two patients with a \(CL_{\text{CR}}\) of <20 ml/min. Imipenem and cilastatin concentrations were measured at steady state on day 5. Mean peak and trough plasma imipenem concentrations were 5.28 ± 1.78 and 1.43 ± 0.76 \(\mu g/ml\) in group I, 6.25 ± 0.78 and 2.50 ± 0.00 \(\mu g/ml\) in group II, and 14.3 ± 0.71 and 6.85 ± 1.06 \(\mu g/ml\) in group III, respectively. Mean peak and trough plasma cilastatin concentrations were 11.8 ± 2.85 and 0.31 ± 0.43 \(\mu g/ml\) in group I, 15.5 ± 2.48 and 2.03 ± 2.05 \(\mu g/ml\) in group II, and 24.5 ± 6.72 and 10.7 ± 5.94 \(\mu g/ml\) in group III, respectively. Mean imipenem \(\text{AUC}_{\text{SS}}\) (area under the concentration-time curve over a dosage interval at steady state) values were 38.7 ± 7.9 \(\mu g \cdot \text{h/ml}\) for group I, 52.3 ± 7.3 \(\mu g \cdot \text{h/ml}\) for group II, and 143.7 ± 11.9 \(\mu g \cdot \text{h/ml}\) for group III. Mean cilastatin \(\text{AUC}_{\text{SS}}\) values were 45.6 ± 12.5 \(\mu g \cdot \text{h/ml}\) for group I, 93.8 ± 51.2 \(\mu g \cdot \text{h/ml}\) for group II, and 217.5 ± 57.6 \(\mu g \cdot \text{h/ml}\) for group III. Imipenem mean apparent body clearance values (normalized to weight) were 3.24 ± 0.78 ml/min for group I, 2.08 ± 0.61 ml/min for group II, and 1.03 ± 0.01 ml/min for group III. Cilastatin mean apparent body clearance values (normalized to weight) were 2.78 ± 0.67 ml/min for group I, 1.43 ± 0.81 ml/min for group II, and 0.71 ± 0.24 ml/min for group III. Imipenem open-lactam metabolite levels were all below the level of detection of the assay (<3.9 \(\mu g/ml\)). There was a progressive increase in plasma imipenem and cilastatin levels and \(\text{AUC}_{\text{SS}}\) and there was a decline in body clearance as renal function declined.

Imipenem is a carbapenem antibiotic with a broad range of antibacterial activity including most gram-negative and gram-positive aerobic and anaerobic organisms. It is readily hydrolyzed by dihydropeptidase I produced in the brush border of the kidney and therefore must be combined with cilastatin, a dihydropeptidase inhibitor, to restore the urinary tract recovery of imipenem (8, 13). Because of the low aqueous solubility of imipenem, imipenem-cilastatin must be diluted to a concentration of 5 mg/ml prior to intravenous administration. A finely milled preparation which, when reconstituted, forms a 200-mg/ml suspension of imipenem suitable for intramuscular administration has been produced. This preparation has been shown to be well tolerated, safe, and effective when administered twice daily to patients with soft tissue infections (12). In the current investigation, we evaluated the disposition of intramuscularly administered imipenem-cilastatin in elderly infected patients with various degrees of renal function.

**MATERIALS AND METHODS**

**Study subjects.** Thirteen subjects with soft tissue infections were enrolled in the study after informed consent was obtained. All subjects were greater than 65 years old and were divided into three groups: group I included eight patients with a creatinine clearance (\(CL_{\text{CR}}\)) of >50 ml/min (range, 51 to 84 ml/min; mean, 65.8 ml/min); group II included three patients with a \(CL_{\text{CR}}\) of 20 to 50 ml/min; and group III consisted of two patients with a \(CL_{\text{CR}}\) of <20 ml/min. Serum creatinine and a 24-h urine collection for the determination of \(CL_{\text{CR}}\) were obtained on the day that plasma was collected for the determination of antibiotic concentrations. Patients were monitored daily for clinical adverse effects. The following laboratory tests were done prestudy, on day 3, weekly, and poststudy for safety assessment: serum creatinine, blood urea nitrogen, aspartate aminotransferase, total bilirubin, alkaline phosphatase, complete blood count with differential, platelet count, and urinalysis. Patients were also assessed daily for local tolerance of the intramuscular injection.

**Study design.** Patients received imipenem-cilastatin (500/500 mg) intramuscularly every 12 h for 5 to 14 days. Each vial containing imipenem-cilastatin was reconstituted with 2 ml of 1% lidocaine and injected into the gluteus maximus with a 2-in. (ca. 5-cm), 21-gauge needle.

**Specimen collection and assay.** Plasma specimens were collected on day 5, when patients were considered to be at steady state. The decision to use day 5 as steady state was based on previously reported half-lives for imipenem in patients administered 250 mg intravenously (with 250 mg of cilastatin); in patients with normal renal function, the imipenem half-life was 1.02 ± 0.16 h, and in patients with severe

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renal impairment (glomerular filtration rate, <10 ml/min/1.73 m²), the imipenem half-life was 3.69 ± 0.51 h (7). Specimens were collected predose and 1, 2, 4, 6, 8, 10, and 12 h postdose. Blood was drawn into heparinized tubes, placed on ice immediately, and centrifuged at 4°C and 1,400 × g for 20 min. Plasma was mixed 1:1 with a stabilizing buffer containing equal volumes of 1 M morpholinoethanesulfonate and ethylene glycol which contained EDTA (5 mM) and ascorbic acid (5 mM) (11, 14). Specimens were stored at −70°C until the time of the assay. Imipenem concentrations were determined by disk agar diffusion with *Bacillus subtilis* ATCC 12439 by a previously described method (11). For imipenem, the coefficient of variation on any given day was 0.99. The day-to-day variation was 0.98 to 1.90. The assay was linear over the range of 0.25 to 2.0 μg/ml. The sensitivity was 0.3 μg/ml. Cilastatin and imipenem open-lactam metabolite concentrations were analyzed by high-pressure liquid chromatography by a previously described method (3, 11).

**Pharmacokinetic analysis.** Steady-state peak concentrations in plasma (C_{pk}), trough concentrations in plasma (C_{tr}), and times to peak concentrations observed (T_{pkobs}) were determined directly from the datum points for each patient. The AUC_{ss} (area under the concentration-time curve over a dosage interval at steady state) was computed with the trapezoidal rule. The apparent total body clearance (CL_{r}/F), uncorrected for bioavailability, was calculated as the quotient of dose/AUC_{ss} and normalized to body weight. Simple linear regression was used to determine the correlation between the CL_{r}/F and the AUC_{ss} with CL_{CR} for both imipenem and cilastatin.

**Statistical analysis.** Demographic information and pharmacokinetic parameters were described with means, standard deviations, and frequencies. Differences among the three groups were analyzed by analysis of variance. For data showing significance with analysis of variance, the Scheffe test for multiple comparisons was used to assess specific differences. Statistical significance was defined to occur at *P* < 0.05.

## RESULTS

**Clinical data.** Demographic data for groups I, II, and III are presented in Table 1. All groups were similar with respect to age and weight. There were significant differences (*P* < 0.05) between the groups with respect to mean serum creatinine levels and CL_{CR}, with serum creatinine levels increasing and CL_{CR} decreasing from group I to group III (Table 1).

All patients tolerated the intramuscular injections without complaints of discomfort or signs of irritation at the injection sites. No clinical adverse reactions or laboratory abnormalities which necessitated discontinuation of the drug occurred in any of the patients.

**Concentrations in plasma and pharmacokinetics of imipenem and cilastatin.** Plasma concentration-versus-time curves for imipenem and cilastatin obtained at steady state (day 5) for all three groups are shown in Fig. 1 and 2. Mean

### Table 1. Patient demographics

<table>
<thead>
<tr>
<th>Group (CL_{CR})</th>
<th>No. of patients (males/females)</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Serum creatinine (mg/dl)</th>
<th>CL_{CR} (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (&gt;50 ml/min)</td>
<td>8 (6/2)</td>
<td>71.8 ± 6.8</td>
<td>70.9 ± 15.0</td>
<td>1.1 ± 0.3^b</td>
<td>65.8 ± 13.6^b</td>
</tr>
<tr>
<td>II (20 to 50 ml/min)</td>
<td>3 (2/1)</td>
<td>73.0 ± 5.0</td>
<td>80.5 ± 18.6</td>
<td>1.3 ± 0.3^b</td>
<td>42.1 ± 7.8^b</td>
</tr>
<tr>
<td>III (&lt;20 ml/min)</td>
<td>2 (1/1)</td>
<td>75.5 ± 2.1</td>
<td>56.8 ± 4.52</td>
<td>2.9 ± 0.4</td>
<td>17.7 ± 0.6</td>
</tr>
</tbody>
</table>

^a Values are means ± standard deviations.

^b *P* < 0.05, versus group III.

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**FIG. 1.** Mean ± standard deviation imipenem concentration in plasma versus time.

**FIG. 2.** Mean ± standard deviation cilastatin concentration in plasma versus time.
C_{pk} and C_{tr} for imipenem and cilastatin and T_{pkobs} are shown in Table 2. In group I (CL_{CR}>50 mL/min), the mean C_{pk} for imipenem and cilastatin were 5.28 ± 1.78 and 11.8 ± 2.85 μg/mL, respectively; the mean C_{tr} were 1.43 ± 0.76 μg/mL for imipenem and 0.31 ± 0.43 μg/mL for cilastatin. The mean T_{pkobs} were 2.64 ± 1.00 h for imipenem and 1.28 ± 0.31 h for cilastatin. Peaks and troughs increased significantly from group I to group III, with the highest plasma imipenem and cilastatin concentrations being achieved in group III (CL_{CR}<20 mL/min). In this group, the mean C_{pk} for imipenem and cilastatin were 14.3 ± 0.71 and 24.5 ± 6.72 μg/mL, respectively; the mean C_{tr} were 6.85 ± 1.06 μg/mL for imipenem and 10.7 ± 5.94 μg/mL for cilastatin. The mean T_{pkobs} for imipenem was also the highest in group III, 4.95 ± 1.34 h.

The AUC_{ss} and CL_{T/F} for imipenem and cilastatin are given in Table 3. The mean AUC_{ss} for both drugs increased significantly from group I to group III; for group I, the mean imipenem AUC_{ss} was 38.7 ± 7.9 μg·h/mL, and for group III, it was 143.7 ± 11.9 μg·h/mL. The mean cilastatin AUC_{ss} values were 45.6 ± 12.5 μg·h/mL for group I and 217.5 ± 57.8 μg·h/mL for group III. The CL_{T/F} decreased from group I to group III for both drugs; for group I, the mean CL_{T/F} for imipenem was 3.24 ± 0.78 mL/min, and for group III, it was 1.03 ± 0.01 mL/min. The mean cilastatin CL_{T/F} values were 2.78 ± 0.67 mL/min for group I and 0.71 ± 0.24 mL/min for group III.

Imipenem open-lactam metabolite levels were below the detection limit of the assay (3.9 μg/mL) in all samples.

**DISCUSSION**

Imipenem-cilastatin was approved by the Food and Drug Administration in 1985 for intravenous administration, and all published pharmacokinetic data regarding both drugs have been derived from that route of administration. Normal volunteers given imipenem-cilastatin (500/500 mg) in the intravenous formulation develop C_{pk} of 35 and 22 μg/mL, respectively, and both drugs have serum half-lives of approximately 1 h (4, 5, 10). For imipenem, 60 to 70% of the intravenous formulation is excreted unchanged in the urine, as compared with approximately 80% for cilastatin. The fate of the remaining 30% of the imipenem dose is unclear, but hepatic or extrahepatic metabolism is assumed to be responsible (4). The remaining 20% of the cilastatin dose is metabolized, presumably by the kidneys (11). Because of the differences between the drugs in renal and metabolic clearance, cilastatin accumulates more than does imipenem when the combination is administered to subjects with reduced renal function. The CL_{T/F} of imipenem in subjects with normal renal function given imipenem-cilastatin (250/250 mg) intravenously has been reported to be 3.42 ± 0.45 mL/kg/min; this value decreases to 0.79 ± 0.10 mL/kg/min in patients with severe renal impairment (glomerular filtration rate, <10 mL/min/1.73 m²); the corresponding values for cilastatin have been reported to be 3.33 ± 1.73 and 0.15 ± 0.05 mL/kg/min (7).

The intramuscular formulation used in this study differs from the commercially available intravenous preparation only in that it is milled more finely and sodium bicarbonate is not present. When the intramuscular powder is reconstituted with 2 mL of sterile water or 1% lidocaine, a suspension of imipenem is formed. Cilastatin, being more water soluble, remains in solution. The use of lidocaine as a diluent does not affect the pharmacokinetics of either drug (9). Plasma imipenem levels were determined after 3 or more days of therapy in 15 patients who had soft tissue infections and who received intramuscular imipenem-cilastatin (500/500 mg) every 12 h. The mean imipenem C_{pk} was 10.7 μg/mL (range, 3.3 to 17.8), and the mean imipenem C_{tr} was 2.1 μg/mL (range, 0.8 to 4.9). All patients had normal renal function (12).

The present study was undertaken to determine whether the pharmacokinetics of intramuscular imipenem-cilastatin would be similar in elderly patients with normal renal function and mild to moderate renal insufficiency. In elderly patients with normal renal function, (group I), mean C_{pk} and C_{tr} were 5.28 ± 1.78 and 1.43 ± 0.76 μg/mL for imipenem and 11.8 ± 2.85 and 0.31 ± 0.43 μg/mL for cilastatin, respectively (Table 2). In the two groups with impaired renal function (groups II and III), for both drugs the C_{pk} and AUC_{ss} rose and the CL_{T/F} fell progressively with decreasing renal function.
Simple linear regression did not show significant correlation between CL\textsubscript{CR} and CL\textsubscript{p}\textsubscript{s} or CL\textsubscript{CR} and AUC\textsubscript{ss} for imipenem and cilastatin. This result is in contrast to that of the study by Gibson et al., in which a significant linear correlation was found between CL\textsubscript{p}\textsubscript{s} and glomerular filtration rate (7). The most likely reason for this discrepancy is that we used a small sample size, so that a full spectrum of renal function was not represented.

Another objective of the study was to determine concentrations in plasma of the imipenem open-lactam metabolite in elderly patients with various degrees of renal function. This metabolite is generated by a nonrenal cilastatin-insensitive metabolic pathway (4). As the parent compound, imipenem, is eliminated by renal mechanisms, the imipenem metabolite can be expected to accumulate when there is renal dysfunction (4).

The clinical reason for our interest in the imipenem open-lactam metabolite was that, if it does accumulate when there is renal dysfunction, it may be responsible for the seizures associated with imipenem-cilastatin administration (1, 2). However, the levels of the imipenem open-lactam metabolite in all of the samples analyzed in this study were below the detection limit of the assay (<3.9 μg/ml). Therefore, the only conclusion that can be made concerning the imipenem open-lactam metabolite is that it did not appear to achieve concentrations in plasma of greater than 3.9 μg/ml during the first 5 days of intramuscular therapy with imipenem-cilastatin (500/500 mg every 12 h).

Although it may be true that the administration of this relatively low dose of imipenem-cilastatin by the intramuscular route does not result in significant imipenem open-lactam metabolite concentrations in plasma, further study with a more sensitive assay and/or an animal model would be useful to confirm this idea and to answer several questions which remain. (i) Does the imipenem open-lactam metabolite, like imipenem, bind postsynaptically to γ-aminobutyric acid receptors in the brain and induce seizures at a much lower concentration than do other beta-lactams (6)? (ii) If it does induce seizures in an animal model, what concentration is achieved? (iii) Does the imipenem open-lactam metabolite achieve low concentrations in plasma (e.g., 0.1 to 3.8 μg/ml) or none at all? (iv) Does the imipenem open-lactam metabolite accumulate to detectable levels during standard intravenous therapy?

The data reported here suggest that dosage reduction of intramuscular imipenem-cilastatin (500/500 mg) in elderly patients with CL\textsubscript{CR} above 50 ml/min is not necessary. A larger number of patients with CL\textsubscript{CR} below 50 ml/min should be studied before the need for dosage reduction can be determined.

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