Pharmacokinetics of Imipenem-Cilastatin in Critically Ill Patients Undergoing Continuous Venovenous Hemofiltration

I. TEGEDER, F. BREMER, R. OELKERS, H. SCHOBEL, J. SCHÜTTLER, K. BRUNE, AND G. GEISSLINGER

Department of Experimental and Clinical Pharmacology and Toxicology, University Erlangen/Nürnberg, 91054 Erlangen, Germany

Received 4 March 1997/Returned for modification 28 July 1997/Accepted 18 September 1997

The pharmacokinetics of imipenem-cilastatin were investigated in 12 critically ill patients with acute renal failure (ARF) managed by continuous veno-venous hemofiltration (CVVH) while receiving a fixed combination of 500 mg of imipenem-cilastatin intravenously three or four times daily. No adverse drug reactions were observed. Plasma and hemofiltrate samples were taken at specified times during one dosing interval, and the concentrations of imipenem and cilastatin were determined by high-performance liquid chromatography. Pharmacokinetic variables were calculated by a first-order, two-compartment pharmacokinetic model for both substances. Total clearances of imipenem and cilastatin (mean ± standard deviations) were 122.2 ± 28.6 and 29.2 ± 13.7 ml/min, respectively, with hemofiltration clearances of 22.9 ± 2.5 and 16.1 ± 3.1 ml/min, respectively, and nonrenal, nonhemofiltration clearances of 90.8 ± 26.3 and 13.2 ± 13.9 ml/min, respectively. Mean imipenem dosage requirements were approximately 2,000 mg/24 h (2,111.8 ± 493.4 mg/24 h). They were calculated in order to achieve an average steady-state concentration of 12 mg/liter to ensure that concentrations in plasma exceeded the MICs at which 90% of intermediately resistant bacteria are inhibited (8 mg/liter) during the majority of the dosing interval. By contrast, the recommended dosage for patients with end-stage renal failure (ESRF) and infections caused by intermediately resistant bacteria is 1,000 mg/24 h. This remarkable difference may be due (i) to differences in the nonrenal clearance of imipenem between patients with ARF and ESRF and (ii) to the additional clearance by the hemofilter. Since the total clearance of cilastatin was low, marked accumulation occurred, and this was particularly pronounced in patients with additional liver dysfunction. Thus, in patients with ARF managed by CVVH, rather high imipenem doses are required, and these inevitably result in a marked accumulation of cilastatin. The doses of imipenem recommended for patients with ESRF, however, will lead to underdosing and inadequate antibiotic therapy.

Imipenem is a carbapenem antibiotic with a broad spectrum of activity against many common pathogens (6) and is thus particularly useful for critically ill patients with septic complications due to unidentified bacteria or bacteria resistant to many other antibiotics. Imipenem is rapidly metabolized by the renal brush border enzyme dehydropeptidase I (DHP I). It is therefore coadministered as a one-to-one combination with the DHP I inhibitor cilastatin, which results in the excretion of about 70% of unchanged imipenem into the urine (25) and a reduction in renal toxicity (18). In healthy volunteers and patients with normal renal function, both agents have almost identical pharmacokinetic properties (8, 9, 26). In patients with renal insufficiency (acute renal failure [ARF] and end-stage renal failure [ESRF]), however, the elimination of both drugs is differently affected, resulting in a much higher accumulation of cilastatin (11). Furthermore, in patients with ESRF total imipenem clearance is more reduced than that in patients with ARF (23). Dose recommendations for patients with renal insufficiency are based mostly on the kinetic data obtained from patients with ESRF (11) undergoing either intermittent hemodialysis (3, 20) and hemofiltration (1) or continuous ambulatory peritoneal dialysis (30). Few data concerning adjustments in patients with ARF (23, 35), but ARF is a common complication in critically ill patients. The preferred device for renal replacement therapy in patients with ARF is the pump-driven continuous veno-venous hemofiltration (CVVH), which allows a constant flow and a high replacement rate (20 to 30 liters/day) and is therefore more effective than the older method, continuous arteriovenous hemofiltration (CAVH), in removing urea nitrogen from the body. Since CAVH depends on the arteriovenous pressure gradient, it may not function optimally in patients with hypotonic episodes or shock (31, 34). Thus, clearance data obtained for certain drugs during CAVH (4, 12, 19, 27, 35) cannot be readily applied to patients undergoing CVVH. The aim of the present study, therefore, was (i) to evaluate the pharmacokinetics of imipenem and cilastatin in patients with ARF undergoing CVVH and (ii) to give practical dosing recommendations applicable to these patients.

MATERIALS AND METHODS

Patients. Thirteen consecutive patients who were admitted to the surgical intensive care unit, who were treated with CVVH for ARF, and who were receiving imipenem-cilastatin (Zienam; Merck Sharp & Dohme, Haar, Germany) for the treatment of a severe life-threatening infection were enrolled in this study. One patient had to be excluded because hemofiltration was interrupted during the collection interval. Patient characteristics and diagnoses are presented in Table 1. Except for patients 1 and 5 (diuresis, 600 ml/24 h), urine production was <150 ml/24 h (Table 1). Patients 4 and 6 had a documented preexisting moderate reduction in renal function. The hemofiltrate creatinine concentrations (C_{crea-HF}) were measured by photometric determinations of the Jaffe reaction by using the Merckotest (Merck, Darmstadt, Germany) reagent kit. The hemofiltration creatinine clearance (HF-CL_{CR}) was determined as HF-CL_{CR} = C_{crea-HF} \times V_{HF}/C_{crea-serum} \times t, where V_{HF} is the hemofiltrate volume, C_{crea-serum} is the serum creatinine concentration, and t is the collection time. Because in the 10 anuric patients renal creatinine clearance (CL_{CR}) was approximately zero, HF-CL_{CR} is approximately equal to the total CL_{CR} in these patients.

The total CL_{CR} for the two patients with residual renal function was calculated...
by the method of Jelliffe and Jelliffe (17), which is suitable for calculating the CL\text{ClCR} in the case of an instable kidney function. HF-CL\text{ClCR} values are depicted in Table 1.

Table 1. Characteristics of 12 critically ill patients with ARF treated by CVVH and with imipenem-cilastatin as a fixed combination

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Sex*</th>
<th>Urine output/8 h (ml)</th>
<th>HF-CL\text{ClCR} (ml/min)</th>
<th>Imipenem dosage (mg/24 h)</th>
<th>Maximal recommended</th>
<th>Calculated</th>
<th>Liver function</th>
<th>Diagnosis or surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>m</td>
<td>200</td>
<td>18.360.8</td>
<td>2.250</td>
<td>2.989.4</td>
<td>B</td>
<td>Liver transplantation</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>m</td>
<td>0</td>
<td>16.3</td>
<td>1.000</td>
<td>1.728.0</td>
<td>A</td>
<td>Laryngectomy and hypopharyngectomy</td>
<td>B</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>m</td>
<td>10</td>
<td>28.4</td>
<td>2.000</td>
<td>1.908.0</td>
<td>B</td>
<td>Liver transplantation</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>76</td>
<td>m</td>
<td>10</td>
<td>16.0</td>
<td>1.000</td>
<td>1.252.8</td>
<td>A</td>
<td>Coronary heart disease, bypass surgery</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>f</td>
<td>200</td>
<td>18.461.3</td>
<td>2.250</td>
<td>2.263.7</td>
<td>A</td>
<td>Aortic and tricuspid valve replacement</td>
<td>A</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>m</td>
<td>50</td>
<td>19.32</td>
<td>1.000</td>
<td>2.710.2</td>
<td>A</td>
<td>Coronary heart disease, bypass surgery</td>
<td>B</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>m</td>
<td>0</td>
<td>15.2</td>
<td>1.000</td>
<td>1.791.1</td>
<td>A</td>
<td>Coronary heart disease, bypass surgery</td>
<td>A</td>
</tr>
<tr>
<td>8</td>
<td>78</td>
<td>m</td>
<td>0</td>
<td>11.5</td>
<td>1.000</td>
<td>2.299.2</td>
<td>B</td>
<td>Retroperitoneal abscess</td>
<td>A</td>
</tr>
<tr>
<td>9</td>
<td>78</td>
<td>m</td>
<td>0</td>
<td>17.1</td>
<td>1.000</td>
<td>1.987.2</td>
<td>B</td>
<td>Hip arthroplasty and iliopectine muscle abscess</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>69</td>
<td>f</td>
<td>0</td>
<td>20.2</td>
<td>1.000</td>
<td>1.831.7</td>
<td>B</td>
<td>Acute duodenal ulcer bleeding, abdominal surgery</td>
<td>B</td>
</tr>
<tr>
<td>11</td>
<td>69</td>
<td>m</td>
<td>20</td>
<td>19.8</td>
<td>1.000</td>
<td>1,952.6</td>
<td>B</td>
<td>Arterial occlusive disease with amputation</td>
<td>B</td>
</tr>
<tr>
<td>12</td>
<td>67</td>
<td>m</td>
<td>0</td>
<td>19.8</td>
<td>1.000</td>
<td>2,868.5</td>
<td>B</td>
<td>Arterial occlusive disease with amputation</td>
<td>B</td>
</tr>
</tbody>
</table>

* m, male; f, female.

Total CL\text{ClCR} calculated from serum creatinine levels.

The recovery of imipenem from plasma and hemofiltrate was approximately 100%; that of cilastatin was 78% from plasma and approximately 100% from hemofiltrate. The intraday coefficients of variation for the concentrations 5, 10, and 15 mg/liter were <0.4 and <4% for imipenem and cilastatin, respectively. The interday coefficients of variation for the same concentrations were <4% (imipenem) and <2% (cilastatin). The lower limit of quantification for imipenem was 0.125 mg/liter in plasma and 0.06 mg/liter in hemofiltrate. The corresponding values for cilastatin were 0.06 mg/liter.

Pharmacokinetic analysis. The pharmacokinetic analysis was performed by using TOPFIT software (14) on an International Business Machines-compatible computer. One- and two-compartment open models were tested to describe the plasma concentration-time profiles of imipenem and cilastatin, and the two-compartment open model was judged to be optimal by the Akaike (36) and Imbimbo et al. (16) information criteria for both drugs. The total area under the concentration-versus-time-curve (AUC) and the area under the first moment curve were calculated by the linear trapezoidal rule. The total body clearance (CL) was obtained by the equation CL = dose/AUC. The sieving coefficient (Sc) was calculated as Sc = C\text{HF}/C\text{Pl}, where C\text{HF} is the concentration of the drug in the hemofiltrate and C\text{Pl} is the corresponding concentration in plasma.

The amount of the drug eliminated by hemofiltration (XHF) was calculated as XHF = AUCHF / VHF. Since in 10 of 12 patients the renal clearance was negligible, the nonrenal clearance (CL\text{nonren}) was obtained by the relationship CL = CL\text{Non} + CL\text{HF}. In the two patients with residual renal function, CL\text{Non} was not calculated. The average steady-state concentration (C\text{SS}) was calculated by the equation C\text{SS} = dose/CL × t, where t is the dosing interval. The clearance data for each patient were used to calculate an imipenem dosing regimen that maintained a C\text{SS} of 12 mg/liter by using the following equation: 24-h dose = CL × 12 mg/liter × 24 h, where CL is in liters per hour.

The 12-mg/liter C\text{SS} was chosen to ensure that the concentration in the plasma of the patient remained above the MIC at which 90% of isolates are inhibited (MIC\text{50} 8 mg/liter) for intermittently resistant Pseudomonas aeruginosa for the majority of the dosing interval. The 24-h dose of cilastatin was calculated correspondingly.

The total mean residence time (MRT) was calculated as MRT = AUMC / AUC, and the volume of distribution at steady state (V\text{ss}) was obtained by V\text{ss} = MRT × CL.

Statistics. The estimated imipenem doses for 24 h were compared with the manufacturer’s recommended doses for patients with reduced renal function. These recommended doses depend on CL\text{Cr}. For patients with a CL\text{Cr} of <20 ml/min, dosages of 500 to 1,000 mg/24 h are recommended. For patients with a CL\text{Cr} of 21 to 40 ml/min, 750 to 2,000 mg/24 h is the recommended dosage, and
patients with a CLCR of 41 to 70 ml/min should be treated with 1,000 to 2,250 mg/24 h (22). For the statistical analysis the highest recommended dosage for each patient according to the patient’s CLCR was used. The unpaired two-tailed Student’s $t$ test was applied, and a value of $P$ of 0.05 was considered statistically significant. The AUC Pls of imipenem and cilastatin were examined for their correlation with total CLCR by using the Pearson correlation coefficient. In order to find out if the CL of imipenem and the CL of cilastatin were dependent on the liver function (function A is normal or slightly elevated glutamic oxalacetic transaminase or glutamic pyruvic transaminase level; function B is markedly elevated total bilirubin level [8 mg/dl] plus one or more markedly impaired other liver function tests), the unpaired two-tailed Student’s $t$ test was applied and a $P$ value of 0.05 was considered statistically significant. Data are expressed as means ± standard deviations (SDs).

RESULTS

Simulated plasma concentration-versus-time curves for imipenem and cilastatin during continued intermittent application of equal doses (500 mg each) are depicted in Fig. 1A and B for 8- and 6-h dosing intervals, respectively. Mean plasma and hemofiltrate concentration-versus-time curves for all patients obtained during the collection interval at steady state are depicted in Fig. 2A (8-h dosing interval) and Fig. 2B (6-h dosing interval). The mean CLs were 122.2 ± 28.6 and 29.2 ± 13.7 ml/min for imipenem and cilastatin, respectively, with CL HFs of 22.9 ± 2.5 and 16.1 ± 3.1 ml/min, respectively, and nonrenal, nonhemofiltration clearances (CLNRs) of 90.8 ± 26.3 and 13.2 ± 13.9 ml/min, respectively (Table 2). After reaching the peak hemofiltrate concentra-

![FIG. 1. Concentrations of imipenem and cilastatin in plasma of critically ill patients during continued intermittent application of equal doses (500 mg each). The patients suffered from ARF and were treated by CVVH. (A) Patients received 500 mg of imipenem and 500 mg of cilastatin every 8 h. (B) Patients received 500 mg of imipenem and 500 mg of cilastatin every 6 h. The MIC₉₀ of susceptible bacteria (< ↓↓↓; 4 mg/liter) intermediately resistant bacteria (↓↓↓↓; 8 mg/liter), and resistant bacteria (↓↓↓; >16 mg/liter) are presented. Samples were collected during one interval after reaching steady-state levels. The concentrations of drugs in plasma are depicted as follows: ●, imipenem; ○, cilastatin.](http://aac.asm.org/)

![FIG. 2. Plasma and hemofiltrate concentration-versus-time curves for imipenem and cilastatin (mean ± SD) in critically ill patients with ARF treated by CVVH. The collection interval during steady state is depicted. A total of 500 mg of imipenem and 500 mg of cilastatin were dissolved in 50 ml of saline and were applied as a 30-min infusion. (A) Patients received 500 mg of imipenem and 500 mg of cilastatin every 8 h. (B) Patients received 500 mg of imipenem and 500 mg of cilastatin every 6 h. The drugs were administered at time zero. Symbols: ■, plasma imipenem concentration; ○, plasma cilastatin concentration; △, hemofiltrate imipenem concentration; δ, hemofiltrate cilastatin concentration.](http://aac.asm.org/)
DISCUSSION

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, imipenem is eliminated by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CL$_{NR}$ of imipenem is reduced from approximately 130 ml/min in patients with normal renal function (26, 33) to approximately 50 ml/min in patients with ESRF (3, 11). A reduction of CL$_{NR}$ rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic data obtained for these patients have been incorporated into drug dosing tables which are used to modify pharmacotherapy in patients with renal failure (2, 32). Little information, however, is available concerning the pharmacokinetic alterations that occur in patients with ARF and under treatment with CVVH. In our patients the CLs of imipenem and cilastatin were approximately 122 and 29 ml/min, respectively, with nonrenal, nonhemofiltration clearances of 91 and 13 ml/min, respectively, and CL$_{NR}$ of 23 and 16 ml/min, respectively. For the CL$_{NR}$ of imipenem, similar data have been reported by Mueller et al. (23). Their assumption of an $X_c$ of 0.8 according to the unbound fraction of the drug in healthy subjects, however, resulted in an underestimation of CL$_{HF}$ (13 ml/min). In this study two different equations were used to calculate the CL$_{HF}$ of the drugs, and both led to similar results (Table 2). The CL$_{HF}$ of imipenem accounts for approximately 20% of the
Because (i) CLNR in patients with ARF is considerably higher with ARF and undergoing CVVH will lead to underdosing usually assumed to be constant over the time of renal failure. However, applying these dose recommendations to patients with ARF and undergoing CVVH will lead to underdosing because (i) CLNR in patients with ARF is considerably higher than that in patients with ESRF and (ii) CVVH clearance values exceed CAVH clearance values.

The imipenem dosage requirements in our patients (2,111.8 ± 493.4 mg/24 h) greatly exceeded the recommended dosage of 1,000 mg/24 h for oligoanuric patients with infections due to intermittently resistant bacteria (11, 22, 35). It has been shown that for β-lactam antibiotics the most appropriate surrogate marker for predicting the outcome is the duration of time that the concentration in plasma exceeds the MIC (15). For more resistant organisms there is an additional concentration dependence for the observed effect (15). Although a postantibiotic effect has been reported for imipenem in vitro, the clinical significance of this effect has not been evaluated (21). Therefore, it is desirable to maintain the concentration of the antibiotic in plasma over the MIC throughout the whole dosing interval. In our patients the concentrations in plasma remained above the MIC for susceptible bacteria (4 mg/liter) for approximately 6 h after they received doses of 500 mg of each of imipenem and cilastatin. This is in accordance with the results of Przechera et al. (27). Thus, a dosing regimen of 0.5 g of each of imipenem and cilastatin four times a day seems appropriate for the treatment of susceptible bacteria in patients with ARF and undergoing CVVH. Even higher doses or more frequent dosing intervals may be needed for some patients if intermediate-resistant bacteria are the cause of the infection. Underdosing with the antibiotic may cause treatment failure, prolongation of hospitalization, rising health care costs, and the emergence of resistant strains.

As has been shown in other studies (11, 19), the nonrenal elimination of cilastatin was low (13.2 ± 13.9 ml/min) in our patients, but it had remarkable variability. Consequently, clearance of drug by CVVH (16.1 ± 3.1 ml/min) became more important in overall drug elimination (65%). Cilastatin clearance during CVVH was remarkably higher than that during CAVH (4 ± 0.8 ml/min) (19), which might explain the more prolonged elimination half-life in anuric patients undergoing CAVH (19). However, even CVVH did not prevent the profound accumulation of cilastatin which led to very high levels of drug in plasma. These were particularly high in patients with an additional liver dysfunction, and the highest cilastatin values were observed in two patients who had received liver transplants. Although no evident toxicity of cilastatin has been reported so far (5, 17, 19) and was not observed in our patients, the inevitable accumulation of this drug should be regarded as undesirable, and some sort of toxicity that is not obvious cannot be ruled out. Hence, the fixed combination of the two drugs is not a favorable treatment, especially for patients with ARF, for whom higher imipenem doses are needed, and for patients with an additional liver dysfunction, in whom cilastatin accumulation is the most pronounced. In our patients the dosage of cilastatin required to reach a C\textsubscript{SSav} of 12 mg/liter was 504.9 ± 235.9 mg/24 h, which was approximately one-fourth of the calculated imipenem dose. However, it is not known if cilastatin concentrations throughout the dosing interval are required to be as high as the imipenem concentrations. It is possible that even smaller doses of cilastatin may be sufficient in order to inhibit DHP I. Therefore, for patients with ARF (treated with CVVH) and for patients with additional liver dysfunction, it seems preferable to administer an appropriate dose of each drug separately. As a practical approach, a 4:1 combination of imipenem-cilastatin might be considered. Alternatively, a carbapenem antibiotic that is not combined with a DHP inhibitor may be used.

**Conclusion.** Therapeutic drug monitoring of imipenem-cilastatin in patients with ARF and treated with CVVH resulted in the following observations. (i) The CLNR of imipenem in patients with ARF is much less reduced than that in patients with ESRF, (ii) clearance by CVVH accounts for 20% of the total CL of imipenem and should be considered in dosing regimens, (iii) marked accumulation of cilastatin occurred, particularly in patients with additional liver dysfunction, and (iv) the dosage requirements for these patients were considerably higher than the doses recommended by the manufacturer. The use of these published dosing recommendations may result in inadequate pharmacotherapy. The results obtained for our patients, however, require confirmation with a larger population-based study.

**ACKNOWLEDGMENTS**

This work was supported by BMBF (01 EC 9403).

We are grateful to the dialysis and intensive care unit nurses. We thank Ute Richter and Beate Layh for excellent technical assistance and Katharina Erb for thorough review of the manuscript.

**REFERENCES**