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, 1Department of Anaesthesiology, 2and IVth Department of Internal Medicine, 3University 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 venovenous 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 intermediate-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 intermittently 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 of the imipenem-cilastatin dose in patients with ARF are available (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 venovenous 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 (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-CLCR) was determined as HF-CLCR = Ccrea-HF × VHF/Crea-serum × t, with VHF is the hemofilter volume, Ccrea-serum is the serum creatinine concentration, and t is the collection time. Because in the 10 anuric patients renal creatinine clearance (CLCR) was approximately zero, HF-CLCR is approximately equal to the total CLCR in these patients.

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

Concomitant drug therapy consisted mainly of antibiotics (n = 13 patients), digitoxin (n = 9), intravenous catecholamines (n = 8), opioids (n = 8) ranitidine (n = 7), midazolam (n = 5), sucralfate (n = 3), and nonopioid analgesics (n = 3). The study was approved by the institutional Ethics Review Board.

**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-CLR_{CVVH} (ml/min)</th>
<th>Imipenem dosage (mg/24 h)</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>18.3±6.0^a</td>
<td>2.250</td>
<td>2.989.4</td>
<td>B Liver transplantation</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 Laryngectomy and hypopharyngectomy</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 Liver transplantation</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 Coronary heart disease, bypass surgery</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>f</td>
<td>200</td>
<td>18.4±6.1^b</td>
<td>2.250</td>
<td>2.263.7</td>
<td>A Aortic and tricuspid valve replacement</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>m</td>
<td>50</td>
<td>19.1±2.2</td>
<td>1.000</td>
<td>2.741.0</td>
<td>A Coronary heart disease, bypass surgery</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>m</td>
<td>0</td>
<td>15.2</td>
<td>1.000</td>
<td>1.797.1</td>
<td>B Coronary heart disease, bypass surgery</td>
</tr>
<tr>
<td>8</td>
<td>78</td>
<td>m</td>
<td>0</td>
<td>11.5</td>
<td>1.000</td>
<td>2.298.2</td>
<td>A Retroperitoneal abscesses</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>A Hip arthropathy and iliospos muscle abscesses</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 Aortic valve replacement and bypass surgery</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 Acute duodenal ulcer bleeding, abdominal surgery</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 Arterial occlusive disease with amputation at the thigh</td>
</tr>
</tbody>
</table>

^a Total CLR calculated from serum creatinine levels.

^b Total CL calculated from serum creatinine levels.

For patients with a CLCR of 21 to 40 ml/min, dosages of 500 to 1,000 mg/24 h are recommended. For patients with a CLCR of 11 to 20 ml/min or a GFR of 20 to 40 ml/min, 750 to 1,500 mg/24 h is recommended. The recommended dose is based on CLCR and serum creatinine level.

**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 CLCR. For patients with a CLCR of <20 ml/min, dosages of 500 to 1,000 mg/24 h are recommended. For patients with a CLCR of 21 to 40 ml/min, 750 to 2,000 mg/24 h is the recommended dosage, and
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. The mean CLs were 122.2 ± 28.6 and 29.2 ± 13.7 ml/min for imipenem and cilastatin, respectively, with CL$_{HF}$ of 22.9 ± 2.5 and 16.1 ± 3.1 ml/min, respectively, and nonrenal, nonhemofiltration clearances (CL$_{NR}$) of 90.8 ± 26.3 and 13.2 ± 13.9 ml/min, respectively (Table 2). After reaching the peak hemofiltrate concentration 1 h after the start of the infusion, the $Sc$ and the CL$_{HF}$ were constant until the end of the dosing interval. Interestingly, 19.8% ± 5.7% of the CL of imipenem was provided by hemofiltration. The corresponding value for cilastatin was 65.2% ± 26.7%. The total amount of the drug eliminated by hemofiltration was calculated as 89.1 ± 26.0 mg (17.8% ± 5.2% of the dose) for imipenem and 303.2 ± 123.6 mg (60.6% ± 24.7% of the dose) for cilastatin. The terminal half-lives for imipenem and cilastatin were 2.9 ± 1.4 and 9.7 ± 4.4 h, respectively. The values of the pharmacokinetic parameters were summarized in Table 2. Since body weight and length are often not exactly known in intensive care unit patients, the pharmacokinetic parameters were not corrected for body mass.

The calculated total daily imipenem requirements in our patients with ARF (2,111.8 ± 493.4 mg) were significantly ($P = 0.002$) higher than the manufacturer’s maximal recommended doses for patients with ESRF (1,409.1 ± 573.1 mg) and infections with intermediately resistant bacteria and with the corresponding CL$_{CR}$ values. They greatly exceeded the recommended dosage of 500 to 1,000 mg/24 h for patients with CL$_{CR}$ of less than 20 ml/min, which can generally be assumed for anuric patients. Our patients received either 1,500 or 2,000 mg/24 h, but none of these patients experienced an adverse

**RESULTS**

Simulated plasma concentration-versus-time curves for imipenem and cilastatin during continued intermittent application of equal doses (500 mg of each of imipenem and cilastatin) 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$_{NR}$ of 22.9 ± 2.5 and 16.1 ± 3.1 ml/min, respectively, and nonrenal, nonhemofiltration clearances (CL$_{NR}$) of 90.8 ± 26.3 and 13.2 ± 13.9 ml/min, respectively (Table 2). After reaching the peak hemofiltrate concentration 1 h after the start of the infusion, the $Sc$ and the CL$_{HF}$ were constant until the end of the dosing interval. Interestingly, 19.8% ± 5.7% of the CL of imipenem was provided by hemofiltration. The corresponding value for cilastatin was 65.2% ± 26.7%. The total amount of the drug eliminated by hemofiltration was calculated as 89.1 ± 26.0 mg (17.8% ± 5.2% of the dose) for imipenem and 303.2 ± 123.6 mg (60.6% ± 24.7% of the dose) for cilastatin. The terminal half-lives for imipenem and cilastatin were 2.9 ± 1.4 and 9.7 ± 4.4 h, respectively. The values of the pharmacokinetic parameters were summarized in Table 2. Since body weight and length are often not exactly known in intensive care unit patients, the pharmacokinetic parameters were not corrected for body mass.

The calculated total daily imipenem requirements in our patients with ARF (2,111.8 ± 493.4 mg) were significantly ($P = 0.002$) higher than the manufacturer’s maximal recommended doses for patients with ESRF (1,409.1 ± 573.1 mg) and infections with intermediately resistant bacteria and with the corresponding CL$_{CR}$ values. They greatly exceeded the recommended dosage of 500 to 1,000 mg/24 h for patients with CL$_{CR}$ of less than 20 ml/min, which can generally be assumed for anuric patients. Our patients received either 1,500 or 2,000 mg/24 h, but none of these patients experienced an adverse

**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 MIC$_{90}$ for susceptible bacteria $<$4 mg/liter), intermediate 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: $\bullet$, imipenem; $\mathbb{1}$, cilastatin.

**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: $\blacksquare$, plasma imipenem concentration; $\blacktriangle$, plasma cilastatin concentration; $\bigcirc$, hemofiltrate imipenem concentration; $\triangle$, hemofiltrate cilastatin concentration.
The CLHF of the drugs, and both led to similar results (Table 2).

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, the CL of imipenem is reduced by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CLNR 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 CLNR rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic alterations were approximately 122 and 29 ml/min, respectively, and CLHFs of 23 and 16 ml/min, respectively. For both drugs, the CLHF accounts for approximately 20% of the renal, nonhemofiltration clearances of 91 and 13 ml/min, respectively. For imipenem, the CLHF of 23 ml/min in patients with ESRF is reduced from approximately 170 ml/min in patients with normal renal function (13, 35). The CL of cilastatin is also reduced from approximately 15 ml/min in patients with normal renal function (13, 35). The CLHF of cilastatin accounts for approximately 8 ml/min in patients with ESRF (13, 35).

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, the CL of imipenem is reduced by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CLNR 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 CLNR rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic alterations were approximately 122 and 29 ml/min, respectively, and CLHFs of 23 and 16 ml/min, respectively. For both drugs, the CLHF accounts for approximately 20% of the renal, nonhemofiltration clearances of 91 and 13 ml/min, respectively. For imipenem, the CLHF of 23 ml/min in patients with ESRF is reduced from approximately 170 ml/min in patients with normal renal function (13, 35). The CL of cilastatin is also reduced from approximately 15 ml/min in patients with normal renal function (13, 35). The CLHF of cilastatin accounts for approximately 8 ml/min in patients with ESRF (13, 35).

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, the CL of imipenem is reduced by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CLNR 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 CLNR rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic alterations were approximately 122 and 29 ml/min, respectively, and CLHFs of 23 and 16 ml/min, respectively. For both drugs, the CLHF accounts for approximately 20% of the renal, nonhemofiltration clearances of 91 and 13 ml/min, respectively. For imipenem, the CLHF of 23 ml/min in patients with ESRF is reduced from approximately 170 ml/min in patients with normal renal function (13, 35). The CL of cilastatin is also reduced from approximately 15 ml/min in patients with normal renal function (13, 35). The CLHF of cilastatin accounts for approximately 8 ml/min in patients with ESRF (13, 35).

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, the CL of imipenem is reduced by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CLNR 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 CLNR rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic alterations were approximately 122 and 29 ml/min, respectively, and CLHFs of 23 and 16 ml/min, respectively. For both drugs, the CLHF accounts for approximately 20% of the renal, nonhemofiltration clearances of 91 and 13 ml/min, respectively. For imipenem, the CLHF of 23 ml/min in patients with ESRF is reduced from approximately 170 ml/min in patients with normal renal function (13, 35). The CL of cilastatin is also reduced from approximately 15 ml/min in patients with normal renal function (13, 35). The CLHF of cilastatin accounts for approximately 8 ml/min in patients with ESRF (13, 35).

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, the CL of imipenem is reduced by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CLNR 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 CLNR rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic alterations were approximately 122 and 29 ml/min, respectively, and CLHFs of 23 and 16 ml/min, respectively. For both drugs, the CLHF accounts for approximately 20% of the renal, nonhemofiltration clearances of 91 and 13 ml/min, respectively. For imipenem, the CLHF of 23 ml/min in patients with ESRF is reduced from approximately 170 ml/min in patients with normal renal function (13, 35). The CL of cilastatin is also reduced from approximately 15 ml/min in patients with normal renal function (13, 35). The CLHF of cilastatin accounts for approximately 8 ml/min in patients with ESRF (13, 35).

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, the CL of imipenem is reduced by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CLNR 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 CLNR rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic alterations were approximately 122 and 29 ml/min, respectively, and CLHFs of 23 and 16 ml/min, respectively. For both drugs, the CLHF accounts for approximately 20% of the renal, nonhemofiltration clearances of 91 and 13 ml/min, respectively. For imipenem, the CLHF of 23 ml/min in patients with ESRF is reduced from approximately 170 ml/min in patients with normal renal function (13, 35). The CL of cilastatin is also reduced from approximately 15 ml/min in patients with normal renal function (13, 35). The CLHF of cilastatin accounts for approximately 8 ml/min in patients with ESRF (13, 35).

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, the CL of imipenem is reduced by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CLNR 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 CLNR rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic alterations were approximately 122 and 29 ml/min, respectively, and CLHFs of 23 and 16 ml/min, respectively. For both drugs, the CLHF accounts for approximately 20% of the renal, nonhemofiltration clearances of 91 and 13 ml/min, respectively. For imipenem, the CLHF of 23 ml/min in patients with ESRF is reduced from approximately 170 ml/min in patients with normal renal function (13, 35). The CL of cilastatin is also reduced from approximately 15 ml/min in patients with normal renal function (13, 35). The CLHF of cilastatin accounts for approximately 8 ml/min in patients with ESRF (13, 35).

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, the CL of imipenem is reduced by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CLNR 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 CLNR rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic alterations were approximately 122 and 29 ml/min, respectively, and CLHFs of 23 and 16 ml/min, respectively. For both drugs, the CLHF accounts for approximately 20% of the renal, nonhemofiltration clearances of 91 and 13 ml/min, respectively. For imipenem, the CLHF of 23 ml/min in patients with ESRF is reduced from approximately 170 ml/min in patients with normal renal function (13, 35). The CL of cilastatin is also reduced from approximately 15 ml/min in patients with normal renal function (13, 35). The CLHF of cilastatin accounts for approximately 8 ml/min in patients with ESRF (13, 35).

Both imipenem and cilastatin are primarily eliminated by the kidneys in patients with normal renal function. In addition, the CL of imipenem is reduced by nonrenal pathways, probably due to metabolism or nonspecific hydrolysis of the molecule in plasma (11, 26). The CLNR 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 CLNR rates in patients with chronic renal insufficiency is known for many drugs (10), and pharmacokinetic alterations were approximately 122 and 29 ml/min, respectively, and CLHFs of 23 and 16 ml/min, respectively. For both drugs, the CLHF accounts for approximately 20% of the renal, nonhemofiltration clearances of 91 and 13 ml/min, respectively. For imipenem, the CLHF of 23 ml/min in patients with ESRF is reduced from approximately 170 ml/min in patients with normal renal function (13, 35). The CL of cilastatin is also reduced from approximately 15 ml/min in patients with normal renal function (13, 35). The CLHF of cilastatin accounts for approximately 8 ml/min in patients with ESRF (13, 35).
total CL, which is considerably higher than the 7% reported to have been obtained with CAVH (19). Published dose recommendations for patients with ARF treated with CAVH (4, 28) are based on an estimate of $CL_{ARF}$ and on an estimate of the $CL_{NR}$ of the drug derived from the literature, which is normally 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) $CL_{NR}$ 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 intermediately resistant bacteria (11, 22, 35). It has been shown that for $\beta$-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 Przeczera 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 intermediately 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), it 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 $C_{S_{CLAV}}$ of 12 mg/liter was 504.9 ± 253.9 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 $CL_{NR}$ 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 dosages 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 thoughtful review of the manuscript.

**REFERENCES**


