Influence of Continuous Venovenous Hemofiltration and Continuous Venovenous Hemodiafiltration on the Disposition of Doripenem

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Doripenem is a synthetic, parenteral carbapenem with a broad spectrum of microbiologic activity that has been approved in over 60 countries for the treatment of adults with complicated intraabdominal infection, complicated urinary tract infection, including pyelonephritis, and nosocomial pneumonia, including ventilator-associated pneumonia (24). Since use of doripenem in critically ill patients in the intensive care unit is anticipated, investigations have been conducted to ascertain the pharmacokinetics of doripenem in patients with various degrees of renal function, including those with end-stage renal disease (ESRD) requiring dialysis (6). A critical step in the development process was characterization of the relationship between the pharmacodynamic response to doripenem and the pharmacokinetic characteristics of the drug. These studies revealed that, like other carbapenems, the pharmacokinetic-pharmacodynamic index of doripenem that was most closely associated with efficacy (90 to 99% reduction in bacterial burden) against Gram-negative bacilli was the maintenance of plasma concentrations above the MICs (%T>MIC) (23).

Continuous renal replacement therapies (CRRTs), such as continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF), are frequently utilized to manage hemodynamically unstable patients, those who are volume overloaded, and those who have acute kidney insufficiency or acute kidney injury (5, 14, 19). Both of these methodologies have been noted to significantly augment the removal of extracellular fluid and waste products, such as urea and creatinine, in those with impaired as well as normal renal function. The total body clearance (CL) of many medications has also been investigated to be enhanced by CVVH and CVVHDF (1, 12, 16, 21). The extent of the clinical impact is primarily dependent on the ultrafiltration rate (Q_{CRRT}) and the sieving coefficient (Sc) for patients receiving CVVH and the combined ultrafiltration and dialysate flow rate (Q_{UFD}) and the saturation coefficient (Sa) for those receiving CVVHDF (12, 21).

The CRRT clearance during CVVH or CVVHDF (CL_{CRRT}) has been investigated for other carbapenems (imipenem, meropenem, ertapenem, and panipenem), and the clearances range from 3.6 to 49.4 ml/min (4, 9–11, 13, 15, 17, 21, 22). In some cases, the stability of the patients’ organ function status and consistency of the delivery of the CRRT were poorly characterized (18). These observations coupled with the broad range of the reported values provided limited confidence for the extrapolation of these findings to doripenem. This study was therefore designed to evaluate the clearance of doripenem and its primary inactive metabolite, doripenem-M-1, while performing controlled CVVH and CVVHDF in dialysis-dependent subjects (DDS). This study enrolled subjects undergoing a stable hemodialysis regimen, be-
cause structured clinical studies requiring the application of stable prescribed therapeutic CVVH or CVVHDF regimens may not be clinically justifiable or feasible in critically ill patients.

MATERIALS AND METHODS

This prospective, open-label, single-dose pharmacokinetic study of doripenem was conducted in dialysis-dependent subjects (DDS) with ESRD and healthy adult volunteers from April to July 2008. The study protocol was reviewed and approved by an independent ethics committee. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practices and all applicable regulatory requirements. All subjects participating in the study provided written informed consent prior to study entry.

Subjects. (i) DDS with ESRD. Adult subjects with ESRD who had been maintained on a standard hemodialysis regimen for at least 1 month preceding prior to study entry. All subjects participating in the study provided written informed consent prior to study entry.

(ii) Healthy volunteers. Each healthy subject had normal renal function (estimated creatinine clearance between 70 and 150 ml/min) as calculated by the Cockcroft-Gault formula (8) and was comparable to the DDS, for which they served as a control, with respect to individual age (±20 years) and weight (±30%). These subjects were all judged to be in good health based on a prestudy medical history, physical examination, vital signs, electrocardiogram, and clinical laboratory test results. They were not allowed to use any medication, except acetaminophen (maximal dose of 1 g per day), for at least 3 days before the study, and no more than 3 g per week) and hormonal contraceptive therapy, starting 21 days before and continuing during the study.

Study design. Subjects who met eligibility criteria were admitted to one of the two clinical research units, Virginia Commonwealth University and Orlando Clinical Research Center, on the evening prior to doripenem administration to confirm their eligibility and verify baseline observations and laboratory measurements which were determined during the screening period. All subjects received doripenem as a single 500-mg, 1-hour intravenous infusion into a forearm vein on the morning of day 1 after an overnight fast. The DDS received doripenem approximately 1 h after the start of their CRRT procedure. Doripenem was infused in the contralateral arm from the dialysis access site or proximal to the CRRT access site when the opposite arm was not available.

CRRT technique. DDS were randomly assigned, using computer-based randomization, to receive either CVVH or CVVHDF (6 subjects in each treatment group). The assigned CRRT study procedure was administered on a day the subject was not scheduled to receive the standard hemodialysis treatment. Thus, each 13-h CRRT procedure was performed in addition to the patient’s regularly scheduled hemodialysis treatments. Venous access was obtained by cannulation of the patient’s hemodialysis arteriovenous fistula or polytetrafluoroethylene graft. The inlet and outlet ports of the filter were connected to the patient and the CRRT apparatus (Prisma; Fresenius Medical Care, New York, NY). This device continuously monitored dialysate, blood, ultrafiltration, and replacement fluid flow rates, as well as arterial and venous pressure, heparin infusion rate, and total net volume removal rate. The same model/brand of hemofilter/dialyzer (polyacrylonitrile AN69 0.9-m2 Prisma M100 dialyzer; Fresenius Medical Care, New York, NY) was used for all CRRT procedures. The CRRT procedure was initiated at a blood flow rate of 125 ml/min. Heparin was infused at a rate of 1,000 units per hour to maintain access and hemofilter patency. A bicarbonate-based dialysate/replacement fluid was utilized in all patients (PrismaMate BGK 2/0 dialysate at 5,000 ml plus 12.5 mg calcium chloride plus 7.5 mg magnesium chloride). In the CVVH procedure, the ultrafiltration rate was maintained at a target of 2 liters per hour to maintain the patient’s fluid status. For CVVHDF, the target ultrafiltrate (UF) and dialysate flow rates were each 1 liter per hour. Ultrafiltrate losses were replaced with replacement fluid at a rate of 1 liter per hour.

Pharmacokinetic assessments. (i) DDS with ESRD receiving CRRT. Serial prefilter and postfilter blood samples (3 ml) were collected in heparinized polypropylene or glass collection tubes by direct venipuncture or via an indwelling catheter from a vein of the opposite arm from which doripenem was administered. No tubes with separation gel were used, and all samples were stored on crushed ice immediately after collection. Samples for the determination of plasma concentrations (Cp) of doripenem and doripenem-M-1, which were collected and processed for the determination of plasma concentrations of doripenem and doripenem-M-1, as described above, immediately prior to the start of the doripenem infusion and at the following times after the start of the infusion: 0.25, 0.75, 1, 1.25, 1.5, 2, 4, 6, 8, and 12 h.

Safety assessment. Safety was assessed throughout the study by evaluating the incidence, severity, onset, resolution, and type of adverse events and their relationship to study drug, as well as changes in clinical laboratory test results, physical examination findings, vital sign measurements, and need for medication or other therapy.

Analytical procedures. Doripenem and doripenem-M-1 concentrations in plasma (Cp), UF (Cp,UF), and UF/D (Cp,UF/D) were quantified by validated assay procedures using reversed-phase chromatography and detection by tandem mass spectrometry (liquid chromatography-triple quadrupole mass spectrometry [LC–MS/MS]). Plasma, Doripenem, doripenem-M-1, and the internal standard samples were extracted from plasma (containing sodium heparin) by protein precipitation. The peak areas were quantified using a Perkin-Elmer series 200 liquid chromatography and an API 5000 series LS–MS–MS instrument (PE Sciex, Foster City, CA) equipped with a Turbo ion spray in the positive ion mode. Calibration curves were obtained by performing a linear regression (weighted 1/x2) on the calibration standards, using Watson 7.0. Peak identification and integration were done using Analyst v1.4.1. The linear standard curve range was 0.1 to 50 μg/ml, with a lower limit of quantitation of 0.1 μg/ml for both doripenem and doripenem-M-1. The interassay precision (coefficient of variation [CV]) for doripenem and doripenem-M-1 in plasma ranged from 4.2% to 16% and 3.7% to 8.1%, respectively, for quality control samples and 1.5% to 9.1% and 1.3% to 5%, respectively, for calibration standards. UF and UF/D. Doripenem, doripenem-M-1, and internal standard samples were diluted with acetonitrile. The samples were vortex mixed and then analyzed by reversed-phase high-performance liquid chromatography (HPLC) using an Atlantis C18 column (Waters, Milford, MA) maintained at 30°C for doripenem and 45°C for doripenem-M-1. The peak areas were quantified using a Perkin-Elmer series 200 liquid chromatograph and an API 5000 series LS–MS–MS instrument (PE Sciex, Foster City, CA) equipped with a Turbo ion spray in the positive ion mode. The linear standard curve range was 0.1 to 50 μg/ml, with a lower limit of quantitation of 0.1 μg/ml for both doripenem and doripenem-M-1. The interassay precision (CV) for doripenem and doripenem-M-1 in plasma ranged from 1.3% to 2.3% and 1.5% to 5.2%, respectively, for quality control samples and 0.7% to 4.6% and 0.8% to 4.2%, respectively, for calibration standards.

Pharmacokinetic analysis. (i) All subjects. Pharmacokinetic parameters for doripenem and doripenem-M-1 were estimated from the observed individual plasma (prefilter values were used for the subjects receiving CRRT) concentration-time data up to 12 hours after the start of the doripenem infusion, via noncompartmental analysis with validated WinNonlin software version 5.2 (Pharsight Corporation). Plasma concentration values that were below the lower limit of quantitation were assigned a value of zero for all pharmacokinetic assessments. The maximum observed plasma concentration (Cmax) and the time the maximum plasma concentration was achieved (Tmax) were determined by inspection of the plasma concentration–time profiles using WinNonlin. The ter-

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Doripenem disposition: impact of CVVH and CVVHDF

TABLE 1. Baseline demographic characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result for CRRT subjects</th>
<th>Result for healthy subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CVVH subjects (n = 6)</td>
<td>CVVHDF subjects (n = 5)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>43.5 (6.89)</td>
<td>43.6 (9.45)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87.1 (29.5)</td>
<td>103 (17.4)</td>
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<tr>
<td>Height (cm)</td>
<td>174 (11.9)</td>
<td>178 (4.75)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3 (6.14)</td>
<td>33.7 (3.69)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (50)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (50)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

* Data are presented as means (standard deviations), except for gender data, which indicate numbers (percentages) of patients.

A total of 25 subjects were enrolled and completed the study, with 23 subjects included in the pharmacokinetic analyses (11 subjects with ESRD receiving CRRT and 12 healthy volunteers). Detailed information regarding patient demographics is given in Table 1. There were no statistically significant differences in gender, age, weight, or BMI score among the dialysis-dependent subjects who received CVVH versus those who received CVVHDF.

Doripenem pharmacokinetics. The plasma concentration-time profiles of doripenem in the subjects receiving CRRT (Fig. 1), after a single 500-mg doripenem infusion, were markedly elevated compared to those in the healthy volunteers. Doripenem AUC_{0–12} was approximately 3-fold or 2.5-fold higher in the CRRT subjects versus the healthy volunteers.

![FIG. 1. Mean (SD) concentration-time profiles of doripenem. The inset presents the concentration-time profile truncated to 12 h after the start of doripenem infusion.](http://aac.asm.org/)
greater for those receiving CVVH (97.6 μg·h/ml) or CVVHDF (72.2 μg·h/ml), respectively, than for the healthy subjects (32.1 μg·h/ml) (P < 0.0001). The observed doripenem plasma concentrations in the healthy subjects were similar to data reported for other healthy subjects receiving doripenem at 500 mg (7). The half-life of doripenem was approximately 4-fold longer for subjects receiving CVVH (mean [SD] of 4.24 [0.56] hours) and CVVHDF (3.87 [0.62] hours) than for healthy subjects (1.29 [0.24] hours). Consistent with these differences in exposure between the populations, the total body clearance of doripenem was significantly reduced in subjects receiving CVVH (27.5% [12.46%]) than during CVVHDF (20.5% [3.99%]). The clearances of doripenem by CVVH and CVVHDF were similar, at 22.2 (4.99) ml/min and 24.5 (5.03) ml/min, respectively. The urea clearances by CVVH and CVVHDF were similar, and these values did not significantly differ from the Cl_CRRT of doripenem (Table 3).

After termination of CRRT, mean doripenem plasma concentrations in the subjects receiving CRRT showed a slight rise followed by a gradual decline until the end of the sampling period (24 h), at which point low but quantifiable concentrations were still detectable, 1.36 μg/ml for CVVH subjects and 0.67 μg/ml for CVVHDF subjects.

**Doripenem CRRT pharmacokinetic parameters.** Doripenem plasma, UF, and UFD concentrations in the subjects who received CVVH were similar over the entire sampling period to concentrations in subjects who received CVVHDF (Fig. 1). The mean (SD) Sc and Sa for doripenem during CVVH and CVVHDF were 0.67 (0.149) and 0.75 (0.163), respectively, indicating that doripenem is extensively removed by both procedures. These calculated values were consistent throughout the sampling periods among all subjects, and no statistically significant trends were evident (Fig. 3). The mean (SD) Ae_CRRT (% per dose) for doripenem was slightly higher during CVVH (27.5% [12.46%]) than during CVVHDF (20.5% [3.99%]). The clearances of doripenem by CVVH and CVVHDF were similar, at 22.2 (4.99) ml/min and 24.5 (5.03) ml/min, respectively. The urea clearances by CVVH and CVVHDF were similar, and these values did not significantly differ from the Cl_CRRT of doripenem (Table 3).

### Table 2. Systemic pharmacokinetic parameters of doripenem and doripenem-M-1

<table>
<thead>
<tr>
<th>Drug and parameter</th>
<th>CVVH subjects</th>
<th>CVVHDF subjects</th>
<th>Result for healthy subjects</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doripenem</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00 (0.97–1.03)</td>
<td>1.00 (0.75–1.00)</td>
<td>1.00 (1.00–1.00)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</td>
<td>24.1 (10.2)</td>
<td>18.9 (3.88)</td>
<td>17.9 (3.17)</td>
<td>0.0001</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→12&lt;/sub&gt; (μg·h/ml)</td>
<td>97.6 (33.4)</td>
<td>77.2 (14.3)</td>
<td>32.1 (6.08)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>V&lt;sub&gt;ss&lt;/sub&gt; (liter/kg)</td>
<td>0.343 (0.199)</td>
<td>0.297 (0.0923)</td>
<td>0.233 (0.0294)</td>
<td>0.1441</td>
</tr>
<tr>
<td><strong>Doripenem-M-1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (h)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00 (0.97–1.03)</td>
<td>1.00 (0.75–1.00)</td>
<td>1.00 (1.00–1.00)</td>
<td></td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/ml)</td>
<td>3.02 (0.818)</td>
<td>2.87 (1.33)</td>
<td>1.80 (0.366)</td>
<td>0.0001</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0→12&lt;/sub&gt; (μg·h/ml)</td>
<td>24.4 (4.58)</td>
<td>21.8 (6.63)</td>
<td>4.73 (0.955)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Clearance of doripenem and doripenem-M-1 by CVVH and CVVHDF<sup>d</sup>

<table>
<thead>
<tr>
<th>Drug/product and parameter</th>
<th>Result for CVVH subjects</th>
<th>Result for CVVHDF subjects</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doripenem</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl&lt;sub&gt;urea&lt;/sub&gt; (ml/min)</td>
<td>26.8 (6.22)</td>
<td>26.7 (8.33)</td>
<td>NA&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are presented as means (SD) unless otherwise noted.

<sup>b</sup> Median (range).

<sup>c</sup> Values represent comparisons between the healthy subjects and the two CRRT groups.

<sup>d</sup> NA, not assessable.
Doripenem-M-1 pharmacokinetics. The maximum doripenem-M-1 concentrations were similar, but the AUC of doripenem-M-1 was significantly greater in subjects receiving CRRT than in healthy subjects (Table 2). Plasma concentrations in the elimination phase for subjects receiving CRRT decreased at a lower rate than those for healthy subjects and did not return to baseline by the end of the CRRT procedure (mean concentrations, 1.61 μg/ml [CVVH] and 1.29 μg/ml [CVVHDF]). After termination of CRRT, doripenem-M-1 plasma concentrations rebounded and remained above those observed at the end of CRRT for the subsequent 12-hour sampling period for subjects receiving CVVH or CVVHDF. The terminal elimination half-life thus could not be reliably estimated for doripenem-M-1 (Table 2).

Doripenem-M-1 CRRT pharmacokinetic parameters. Doripenem-M-1 exposure in plasma during the CRRT procedure, AUC0–12, was approximately 5-fold greater for the DDS (24.4 [4.58] μg · h/ml during CVVH and 21.8 [6.63] μg · h/ml during CVVHDF) than for the healthy subjects (4.73 [0.96] μg · h/ml) (Fig. 2). The mean (SD) Sc and Sa for doripenem-M-1 during CVVH and CVVHDF, respectively, were 0.817 (0.109) and 0.928 (0.174), indicating that doripenem-M-1 is extensively removed by both procedures. These calculated values were consistent throughout the sampling periods among all subjects, and no statistically significant trends were evident (Fig. 3). The mean (SD) AeCRRT (% per dose) for doripenem-M-1 was slightly higher during CVVH (10.1% [3.82%]) than during CVVHDF (8.44% [1.65%]). The clearances of doripenem-M-1 by CVVH and CVVHDF were similar, i.e., 27.1 (3.59) versus 30.3 (4.97) ml/min, respectively (Table 3).

Safety and tolerability. Treatment-emergent adverse events were reported in 6 subjects: 3 healthy volunteers, 2 subjects receiving CVVH, and 1 subject receiving CVVHDF. All of these events were either mild or moderate in severity, and all resolved by the end of the study. Three events, acute pancreatitis, acute abdominal pain, and hyperkalemia, were assessed by the investigator as related to study drug. The event of acute pancreatitis was reported on day 1 in a healthy volunteer, resolved within 2 days, and was confounded by predisposing conditions, including the possibility of a preexisting biliary stone in a middle-aged woman with a BMI of 30.5 kg/m² and a history of hypercholesterolemia. The abdominal pain, described as stomach cramps, occurred in a healthy male volunteer on day 1 and resolved spontaneously after 2 h. The event of hyperkalemia was reported the day after study drug administration in a subject with ESRD with a medical history of hyperkalemia. There were no deaths or serious adverse events reported in the study.

DISCUSSION

The disposition of several carbapenems during CRRT has been reported in single case reports or as a series of clinical cases. Unfortunately, it is difficult, if not impossible, to control the variables that may affect the clearance of carbapenems in acutely ill patients. In this study, we prospectively measured the systemic pharmacokinetics of doripenem and its primary metabolite, doripenem-M-1, in DDS with ESRD undergoing a session of CRRT. The mean CL and CLNR in these subjects were similar to those in previous reports of subjects with ESRD (6) and significantly lower than values observed in healthy subjects (7). No significant differences in Vss were noted. The impacts of two CRRT procedures, CVVH and CVVHDF, on the disposition of doripenem and doripenem-M-1 were also rigorously assessed. The mean Sc and Sa for doripenem were comparable with those from previous reports of imipenem and meropenem, in which the same hemofilter was used (10, 13, 21). The CLCRRT of doripenem accounted for 25 to 32% of the observed CL, and the mean values ranged from 82 to 92% of simultaneous CLUREA values, clearly indicating that either mode of CRRT has a marked effect on the disposition of doripenem, which needs to be accounted for with an increase in the daily doripenem dosage.
Many investigations of the pharmacokinetics of carbapenems in critically ill individuals have been published in the last 10 to 15 years. The results of these investigations suggest that there is marked variability between the agents within the class and that critical illness and/or acute impairment of kidney function is associated with a reduction in renal, as well as nonrenal, clearance. The reduction in renal clearance of imipenem and meropenem is correlated with the patient’s degree of residual renal function and independent of the duration of the renal injury, i.e., whether the patient has acute or chronic kidney disease. The reduction in nonrenal clearance of these agents in subjects with acute impairment of kidney function is significant relative to clearance in those with normal renal function, but clearance is not as low as the values which have been observed in subjects with ESRD who are dialysis dependent. The renal and nonrenal clearance of doripenem in stable chronic kidney disease patients, and those who are dialysis dependent, has been noted to be lower than that observed in healthy subjects; the results of these investigations can be utilized to estimate the clearance of doripenem (6, 7).

Continuous replacement renal therapies have emerged as the foundational renal replacement therapies for the critically ill patient (5, 19). CVVH, as the preferred therapy for the management of fluid-overloaded patients and at ultrafiltration rates greater than 1 liter/h, has also proven to be an efficient means of removing accumulated waste products. CVVHDF augments convection with diffusion and as a result is considered by some to be the most efficient method of CRRT. In clinical practice, these therapies are tailored to the individual patient’s needs by modification of the blood flow and ultrafiltration, dialysate, and replacement fluid flow rates, as well as the hemofilter or dialyzer. Results of recent investigations suggest that although the achieved clearances of urea, a marker of renal insufficiency and CRRT efficiency, may vary 2- to 3-fold, the delivery of an increased therapeautic regimen was not associated with an improvement in clinical outcomes (2, 20).

The influences of CRRT on the removal of drugs have also been noted to be markedly variable, although there is a clear trend in the last 10 to 15 years toward higher clearances with all agents that have been evaluated throughout this time period (3, 9, 12, 21). The clearances of imipenem by CVVH ranged from 6.5 to 13.3 ml/min in the 1990s and have increased to 22.9 to 36.0 ml/min during the last decade (9, 10, 21). This increase is in part due to the utilization of larger-surface-area hemofilters and higher ultrafiltration rates. The CVVHDF clearance of imipenem has generally been greater than that observed with CVVH; values have ranged from 18.7 to 57 ml/min, with higher values being observed in patients who had greater Q

The disposition of meropenem has been evaluated extensively in critically ill patients with creatinine clearances ranging from 0 to 118 ml/min (13, 15, 17, 21). The total body clearances reported by the nine investigative teams which have assessed the influence of CVVH and/or CVVHDF vary widely (52 to 1,064 ml/min) and thus are relatively noninformative in terms of application of the data to prospective patient care situations. Focusing on those studies in patients with CLcr less than 70 ml/min dramatically reduces the variability in CL, to 52 to 143 ml/min (13, 17, 21). The mean nonrenal clearances from a subgroup of 5 investigations of 38 patients ranged from 35 to 59 ml/min and are comparable to the values observed in individuals with normal renal function (Table 2). The CRRT procedure clearances are higher with CVVHDF than with CVVH, and when the same hemofilter was utilized (AN69 with a surface area of 0.9 m²), the values ranged from 27.0 to 38.9 ml/min and 17.2 to 27.0 ml/min, respectively. The mean (SD) saturation and sieving coefficients derived from these investigations were less variable, 0.92 (0.05) and 0.74 (0.13), respectively, and thus these parameters may be the most useful measure of CRRT efficiency for prospective utilization.

Since the dialysis-dependent subjects evaluated in this study had chronic renal disease and were not acutely or critically ill but were anuric (n = 9) or had minimal residual renal function (urine output less than 300 ml/day) (n = 3), the systemic pharmacokinetics of doripenem were expected to be, and were,
similar to previous observations in ESRD patients (Fig. 3). The ability to maintain constant CVVH and CVVHDF procedures throughout the observation period facilitated the rigorous characterization of the clearance, Sc, and Sa of doripenem by these two CRRTs. The doripenem Sc and Sa were stable over the entire observation period throughout the observation period facilitated the rigorous ability to maintain constant CVVH and CVVHDF procedures similar to previous observations in ESRD patients (Fig. 3). The doripenem Sc and Sa were stable over the entire observation period facilitated the rigorous ability to maintain constant CVVH and CVVHDF procedures similar to previous observations in ESRD patients (Fig. 3).

The primary challenge to the clinician’s determination of the optimal individualized dosage regimen is thus the broad range of residual renal and other organ functions that one may encounter in the critically ill patient population. Indeed, the composite organ function of one critically ill population may bear little resemblance to that of another population. The clinician is thus faced with the need to evaluate and quantify the functionality of each relevant organ system, as well as the influence of therapeutic interventions, such as CRRT, to arrive at the optimal dosage regimen for the patient. This investigation provides the foundational knowledge of the influence of CVVH and CVVHDF on the disposition of doripenem, which can be used to guide the initiation of therapy and to perform additional analysis to establish an optimal dosage regimen for patients treated with doripenem and undergoing these modalities of CRRT.

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REFERENCES