Meropenem removal in critically ill patients undergoing sustained low-efficiency dialysis (SLED)

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Abstract

Background. The purpose of this study was to examine the removal of meropenem during an 8-h sustained low-efficiency dialysis (SLED) session. Using a minimum inhibitory concentration (MIC) of 2 μg/mL as our reference point, we also evaluated the therapeutic adequacy of dosing meropenem as 1 g every 12 h during SLED.

Methods. This was a prospective, open-label study involving 10 intensive care unit patients with renal failure needing SLED. Meropenem was dosed as 1 g every 12 h. To ensure a steady state, the patients received at least two doses prior to the study. SLED was initiated at least 2 h after the last meropenem dose, and each session was at least 8 h. Blood samples were collected during SLED at 0, 2, 4 and 8 h. The 8-h sample approximated the trough level. After centrifuging the samples, the supernatants were analysed by high-performance liquid chromatography.

Results. Most patients were male with a mean age of 63.7 years and a mean weight of 88.9 kg. The SLED prescription was based on each patient's needs, and the blood flow, dialysate flow and ultrafiltration rates varied by up to 150 mL/min. The mean reduction of plasma meropenem concentration was 79.1 ± 7.3%, and the mean half-life was 3.6 ± 0.8 h during the 8-h SLED. Significantly more meropenem was removed in the first 4 h of SLED compared with the rest of the sessions. The mean plasma trough concentration was 4 ± 1.6 μg/mL.

Conclusions. Meropenem was significantly removed from the blood compartment during SLED. Dosing 1 g of meropenem every 12 h during a typical 8-h SLED session maintains adequate plasma concentrations.

Keywords: dialysis; ICU; meropenem; renal failure

Introduction

Understanding the removal of antibiotics during prolonged dialysis is crucial in the care of intensive care unit (ICU) patients. Meropenem is a synthetic broad spectrum parenteral carbapenem antibiotic that is used in the treatment of severe infections caused by Gram-positive and Gram-negative organisms, including beta-lactamase producers and anaerobes. Achieving and maintaining therapeutic plasma meropenem levels are essential to the survival of critically ill patients with sepsis. The current literature addresses meropenem clearance and dosing regimens in patients receiving intermittent haemodialysis (IHD) and continuous renal replacement therapy (CRRT). Studies have shown that 50% of meropenem in the blood compartment is eliminated by IHD and between 13% and 53% by CRRT [1]. If meropenem is not re-dosed prior to its therapeutic trough level, then patients have windows of susceptibility to the infectious organisms.

Sustained low-efficiency dialysis (SLED), also known as extended daily dialysis (EDD), is a hybrid dialysis technique developed at the University of Arkansas in 1998 that...
combines standard IHD equipment from Fresenius but aims for slower flow and ultrafiltration rates than IHD. SLED is similar to CRRT in its beneficial haemodynamic effects in critically ill patients but is more cost-effective than CRRT [2,3].

There are limited data on the newer antimicrobials and their pharmacokinetics in the setting of renal replacement therapy in the ICU setting. A number of studies have identified possible problems in adequately dosing antibiotics in SLED; they include discrepancies in the recommended antibiotic dosing by manufacturers, assuming IHD parameters, and the actual needs of patients who received SLED. One study demonstrated that ICU patients in acute renal failure treated with EDD require a standard dose of ertapenem [1 g daily as opposed to the recommended 0.5 g daily for end-stage renal disease (ESRD)] in order to maintain adequate free, protein-unbound antibiotic levels [4]. The removal of a single dose of linezolid (typically administered 600 mg every 12 h) during an 8-h SLED session in ICU patients with acute renal failure resulted in subtherapeutic antibiotic levels at the end of SLED [5]. These studies support the notion that the pharmacokinetics of antibiotics is significantly altered in septic patients with multi-organ failure.

In this preliminary study, we sought to determine the reduction in meropenem plasma levels and the adequacy of dosing the antibiotic as 1 g every 12 h in a cohort of ICU patients receiving SLED. In doing this, we hope to refine our dosing protocols to better treat our patients.

Materials and methods

Study design
This prospective study was approved by the Montefiore Medical Center Institutional Review Board Committee.

Patients
Ten adult ICU patients with acute or chronic renal failure were evaluated for the study. Patients were eligible if they required SLED for 8 h or longer and if they were at least 18 years of age, oliguric with urine output <400 mL/day, and required meropenem therapy for a documented or suspected infection. Patients were enrolled in the study after informed consent was obtained from the patient or the patient’s legal representa-

tive. Exclusion criteria included a history of severe penicillin allergy (i.e. anaphylaxis or haemodynamic instability), pregnancy or if meropenem therapy was not indicated.

Meropenem therapy
Meropenem was administered as a 1-g intravenous infusion over 30 min. To ensure a steady-state plasma concentration, the patients received at least two doses as per dosing protocol prior to the start of the study. SLED was initiated at least 2 h and no later than 4 h after the second meropenem dose to ensure that adequate drug levels are achieved.

Renal replacement therapy—SLED
The decision to initiate SLED in each patient was made by the attending nephrologist. SLED was performed using the Fresenius 2000 K machine with an AV400 polysulfone dialyser (sieving coefficient for vitamin B12 = 1, and surface area = 0.7 m²). Blood flow rate (Q_B), dialysate flow rate (Q_D) and ultrafiltration rate (UFR) were determined based on patients’ needs.

Blood sample collection
A total of four 5-mL blood samples were obtained from each patient at time 0, 2, 4 and 8 h after SLED was initiated. The samples were drawn from the arterial line and collected into a serum separator tube. The samples were centrifuged at 3500 rpm (IEC MB centrifuge) within 10 min, and the supernatants were separated and stored in a −70°F freezer until final analysis. Meropenem levels were analysed using high-performance liquid chromatography by an outside laboratory (Hartford Hospital, CT).

Data analysis
The extent of meropenem removal from the blood during a SLED session was calculated and expressed as percentage of concentration reduction. All data are expressed as mean ± standard deviation (M ± SD), and paired Student’s t-test with a one-tailed distribution was used to compare the data when appropriate. Serum meropenem levels reported for each patient were also analysed using a simplified one-compartment model that assumes first-order pharmacokinetics as described by Winter [6]. The half-life of meropenem clearance during a SLED session was estimated using this model.

Results
Ten (two females and eight males) critically ill patients with oliguric or anuric renal failure were included in this study. Their mean age was 63.7 ± 11.7 years, and mean weight was 88.9 ± 21.5 kg. The characteristics of individual patients are given in Table 1. Q_B ranged from 100 to 250 mL/min (M ± SD: 160.0 ± 45.9 mL/min), Q_D ranged from 100 to 200 mL/min (170.0 ± 42.2 mL/min) and UFR ranged from 20 to 200 mL/h (129.5 ± 58.5 mL/h) (Table 2). All patients received SLED for 8 h on the day the blood samples were collected.

Mean meropenem plasma concentrations measured at time 0, 2, 4 and 8 h were 20.7 ± 8.2, 9.8 ± 3.7, 6.4 ± 1.9 and 4.0 ± 1.6 μg/mL, respectively (Table 2, Figure 1). The 8-h blood samples were collected near the end of the 12-h dosing interval (trough) for all patients. Mean serum meropenem concentrations were reduced by 79.1 ± 7.3% during the 8-h SLED session with an estimated mean serum half-life of 3.6 ± 0.8 h (Table 2). Meropenem was eliminated from the blood compartment more rapidly during the early stage of SLED as compared to the late stage. An average of 66.5 ± 11.1% versus 36.8 ± 18.3% of meropenem was cleared from the blood during the first 4 h and the last 4 h of SLED, respectively (P = 0.001).

Discussion
Meropenem is a carbapenem antibiotic with a molecular weight of 437.52 Da. Unlike imipenem, it is not hydrolysed by human renal dehydropeptidase-I and thus does not require the administration of dehydropeptidase-I enzyme inhibitor such as cilastatin. Meropenem is minimally bound to plasma proteins and is filtered at the level of the glomerulus and secreted into the renal tubules. It is then excreted in the urine unchanged. In subjects with normal renal function, the elimination half-life of meropenem is ~1 h, and the volume of distribution at a steady state ranges from 11.7 to 26.6 L as it is widely distributed into different tissue compartments. In patients with compromised renal function, the half-life can range from 1.5 to
The clearance of meropenem is linearly correlated with creatinine clearance (CL\text{CR}), and non-renal excretion increases as renal function declines [9]. Meropenem is metabolized through an unknown mechanism into an open ring metabolite and is secreted into the biliary tract [10]. Non-renal clearance is responsible for 20% of the total meropenem elimination and rises to 50% in patients with CL\text{CR} of <30 mL/min [1,10].

SLED is a hybrid dialysis modality that uses standard Fresenius IHD equipment but aims to clear solutes over a prolonged period of time. SLED is slightly more efficient than CRRT in that it utilizes a higher Q\text{D}, but like IHD, it can be administered intermittently thereby accommodating patients’ needs (e.g. enabling patients to leave the ICU for diagnostic testing and therapeutic procedures). It also lessens the volume fluxes associated with ultrafiltration during IHD that can contribute to haemodynamic instability.

### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>BMI</th>
<th>Clinical condition</th>
<th>Mechanical ventilation</th>
<th>Vasopressors</th>
<th>Liver function</th>
<th>Platelet count</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>F</td>
<td>72</td>
<td>107.8</td>
<td>46.7</td>
<td>Sepsis, bacteraemia Multi-lohar pneumonia Gram-negative sepsis</td>
<td>Yes</td>
<td>Yes</td>
<td>Abnormal: elevated transaminases</td>
<td>Normal</td>
</tr>
<tr>
<td>B</td>
<td>F</td>
<td>72</td>
<td>61.9</td>
<td>26.8</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>C</td>
<td>M</td>
<td>55</td>
<td>97.7</td>
<td>31.8</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Abnormal: coagulopathy, hyperbilirubinemia, elevated transaminases</td>
<td>Initially normal but then developed thrombocytopenia</td>
</tr>
<tr>
<td>D</td>
<td>M</td>
<td>73</td>
<td>70.0</td>
<td>N/A</td>
<td>Necrotizing pneumonia secondary to Aspergillus Cardiogenic shock</td>
<td>Yes</td>
<td>Yes</td>
<td>Abnormal: elevated transaminases</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>E</td>
<td>M</td>
<td>62</td>
<td>88.2</td>
<td>22.4</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Abnormal: mild transaminase elevation</td>
<td>Normal</td>
</tr>
<tr>
<td>F</td>
<td>M</td>
<td>81</td>
<td>100.0</td>
<td>29.2</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Abnormal: mild transaminase elevation, mild hyperbilirubinemia</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>G</td>
<td>M</td>
<td>59</td>
<td>126.6</td>
<td>37.6</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Abnormal: elevated transaminases and hyperbilirubinemia</td>
<td>Normal</td>
</tr>
<tr>
<td>H</td>
<td>M</td>
<td>53</td>
<td>84.5</td>
<td>Yes</td>
<td>Coronary artery disease</td>
<td></td>
<td>Yes</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>I</td>
<td>M</td>
<td>68</td>
<td>61.1</td>
<td>56.9</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Abnormal: hyperbilirubinemia</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>J</td>
<td>M</td>
<td>42</td>
<td>95.0</td>
<td>N/A</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Abnormal: elevated transaminases, coagulopathy, hyperbilirubinemia</td>
<td>Thrombocytopenia</td>
</tr>
</tbody>
</table>

### Table 2. Serum concentrations (with mean ± standard deviation) of meropenem at each time interval in patients receiving SLED

<table>
<thead>
<tr>
<th>Patient</th>
<th>Q\text{B} (mL/min)</th>
<th>Q\text{D} (mL/min)</th>
<th>Ultrafiltration rate (mL/h)</th>
<th>Urine output (mL/day)</th>
<th>Serum meropenem concentrations (μg/mL) while on SLED</th>
<th>% decrease in serum meropenem</th>
<th>Half-life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>200</td>
<td>200</td>
<td>223</td>
<td>21 11.6 7.7 3.7 82.4% 3.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>150</td>
<td>100</td>
<td>200</td>
<td>100</td>
<td>33 15.6 9.6 7 78.8% 3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>150</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>13.9 7.4 6.4 3.3 76.3% 3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>100</td>
<td>200</td>
<td>100</td>
<td>35</td>
<td>32.1 6.9 6.9 2.1 93.5% 2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>150</td>
<td>200</td>
<td>100</td>
<td>0</td>
<td>9.4 8.2 5.1 2.8 70.2% 4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>150</td>
<td>200</td>
<td>160</td>
<td>22</td>
<td>22 14 5.1 4.7 78.6% 3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>250</td>
<td>150</td>
<td>100–150</td>
<td>0</td>
<td>10 3.9 2.8 2.3 77.0% 3.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>200</td>
<td>200</td>
<td>180</td>
<td>22</td>
<td>22 13.1 7.9 5.3 75.9% 3.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>0</td>
<td>26.1 8.1 5.4 3.1 88.1% 2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>200</td>
<td>200</td>
<td>20</td>
<td>0</td>
<td>17.6 8.8 7 5.3 69.9% 4.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean ± standard deviation: 20.7 ± 8.2 9.8 ± 3.7 6.4 ± 1.9 4.0 ± 1.6 79.1 ± 7.3% 3.6 ± 0.8

Also shown are the Q\text{B} and Q\text{D} for each patient, the percent decrease in serum concentrations of meropenem (with mean ± standard deviation) and half-life (with mean ± standard deviation).
Unlike CRRT, SLED does not require chronic anticoagulation [2,3]. The intermittent and prolonged function of SLED coupled with its ability to efficiently clear urea and other small solutes may complicate the administration of antibiotics in septic ICU patients.

The half-life of meropenem in patients on IHD is 2.9 h [2], and IHD with cuprohane membranes eliminates 50–70% of meropenem during a typical IHD session [9]. The half-life of meropenem in patients undergoing continuous veno-venous haemodialysis (CVVH) or haemodiafiltration (CVVHDF) ranges between 2.3 and 8.7 h [1,11]. In the setting of CVVH/CVVHD, the meropenem clearance is dependent largely on specifics of the modality prescription; this explains the broad range of half-lives encountered.

The manufacturer's dosing recommendations depend on CL\textsubscript{CR} and are as follows: CL\textsubscript{CR} of <10 mL/min, 500 mg every 24 h; CL\textsubscript{CR} of 10–25 mL/min, 500 mg every 12 h; and CL\textsubscript{CR} of 26–50 mL/min, 1 g every 12 h. Some studies showed that it is necessary to increase the recommended doses of meropenem dosing by >100% in patients undergoing continuous dialysis [11–13]. The primary purpose of our study was to determine if dosing meropenem as 1 g every 12 h is adequate to achieve and maintain therapeutic plasma levels in severely ill ICU patients on SLED. Using the minimum inhibitory concentration (MIC\textsubscript{90}) = 2 μg/mL for susceptible \textit{Pseudomonas aeruginosa} as our reference point, we found that the mean serum meropenem concentration remained greater than the MIC\textsubscript{90} for 100% of the dosing interval while on SLED (mean trough level 4.0 ± 1.6 μg).

Kielstein et al. utilized EDD (using a polysulfone high-flux dialyser) to study meropenem clearance [14]. They administered 1 g of meropenem 6 h prior to the start of an 8-h EDD session and followed meropenem levels before, during and after EDD (meropenem was not re-dosed). Using a first-order pharmacokinetic model and Q\textsubscript{D} and Q\textsubscript{B} that were similar to ours (160 mL/min), they found that the half-life of meropenem on EDD was 3.7 h and 51% of the drug is removed during one session. Our study shows that a larger percentage of meropenem is removed by Hour 8 of SLED. Kielstein et al. concluded that dosing 1 g of meropenem prior to the EDD session resulted in subtherapeutic plasma meropenem levels at 8 h, and thus recommended a dosing of 500 mg–1 g every 8 h. In our study, however, the plasma meropenem levels for all of our patients were above the MIC for the entire duration of the SLED session (i.e. for ~12 h after the last dose of the antibiotic).

We found that significantly more meropenem is eliminated during the first half of the SLED (66.5 ± 11.1% versus 36.8 ± 18.3%, P = 0.001). While this is of interest, it does not deter from the clinical objective of this study which is to clarify an adequate dosing regimen for meropenem. The more efficient elimination of the drug in the initial period does not result in subtherapeutic levels. Although the removal of meropenem is non-linear, we used a simplified linear pharmacokinetic model and estimated that the mean plasma half-life was ~3.6 ± 0.8 h.

Our preliminary study has several limitations. Firstly, this is an observational study. Secondly, a first-order pharmacokinetic model was used in order to simplify the final analysis, though the removal of meropenem by SLED did not exactly coincide with this model (i.e. significantly more meropenem was removed in the first half of the SLED session as compared with the second half). Also, the Q\textsubscript{D} and Q\textsubscript{B} were variables for each patient but not significantly. We were not able to account for non-renal metabolism of meropenem using this study design. Since our purpose was to elucidate drug dosing in a clinical setting, we felt that measuring serial levels at set time intervals was practically useful. Lastly, we used MIC\textsubscript{90} = 2.0 μg/mL for susceptible \textit{Pseudomonas aeruginosa}, and our dosing regimen may not apply to more resistant strains.

Ensuring that meropenem is appropriately dosed in septic ICU patients on renal replacement therapy is paramount.
to their care, especially when monitoring meropenem levels is not a practical option for many medical centres. After dosing 1 g of meropenem, we found that the plasma meropenem levels for all of our patients remained above the MIC for the entire duration of the SLED session (for at least $\sim 12$ h). We therefore suggest dosing meropenem at 1 g every 12 h in this population of ICU patients on SLED.

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Dinucleoside polyphosphates: newly detected uraemic compounds with an impact on leucocyte oxidative burst

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Abstract

Background. Dinucleoside polyphosphates (NPnN) have pathophysiologic roles in cardiovascular disease and are newly detected uraemic retention solutes. They were retrieved in human plasma, tissues and cells. Although their impact on several cell systems involved in vascular damage (endothelium, smooth muscle cells and thrombocytes) has been evaluated, their effect on different types of leucocytes has never been studied.

Methods. This study evaluates, for the first time, the impact of NPnN on monocyte, granulocyte and lymphocyte oxidative burst activity at baseline and after stimulation with N-formyl-methionine-leucine-phenylalanine (fMLP) and phorbol 12-myristate 13-acetate (PMA) in whole blood. Diadenosine triphosphate (Ap3A) to diadenosine hexaphosphate (Ap6A) were tested to investigate the effect of the number of phosphate groups on reactive oxygen species (ROS) production. The effect of the type of nucleoside