Penetration of Ertapenem into Muscle Measured by In Vivo Microdialysis in Mechanically Ventilated Patients

I. Boyadjiev,1 A. Boulamery,2 N. Simon,2 C. Martin,1 B. Bruguerolle,2 and M. Leone1*

Service d’anesthésie et de réanimation, Hôpital Nord, Assistance Publique—Hôpitaux de Marseille, Université de la Méditerranée, 13015 Marseille, France;1 and Laboratoire de Pharmacologie Médicale et Clinique, Faculté de Médecine de Marseille, 27 Bd. J. Moulin, F13385 Marseille Cedex 5, France2

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Ertapenem at 1 g once daily has been suggested to be underdosed in intensive care unit (ICU) patients to attain optimal concentrations in target tissues. Therefore, our study aimed to assess the kinetics of ertapenem in plasma and skeletal muscle in ICU patients using microdialysis. Average muscle-free ertapenem concentrations were above the MIC values of targeted pathogens. In a few patients, the concentrations were below the MIC values. The clinical efficiency of ertapenem at 1 g once daily should be evaluated in a large population of ICU patients.

Ertapenem at 1 g once daily has been approved for the treatment of complicated intraabdominal, complicated skin and skin structure, acute pelvic, complicated urinary tract, and community-acquired infections (13, 15). This has been supported by studies of tissue penetration in healthy volunteers (2, 8). However, few studies have detailed ertapenem penetration in the intensive care unit (ICU) patient (1, 3, 4).

The pharmacokinetics of drugs are modified in ICU patients due to the large daily fluid balance, acute changes in body weight, hypoalbuminemia, edema, and low hematocrit values, resulting in marked changes in elimination half-life (t1/2), volume of distribution (V), and clearance (CL) (12, 14). In patients with ventilator-associated pneumonia using the recommended daily dose (1 g) of ertapenem, bactericidal targets could not be attained for MIC values above 0.5 mg · liter⁻¹ (4). This finding is in agreement with that of previous studies dealing with time-dependent antibiotics in ICU patients (6, 12). This leads to the hypothesis that ertapenem at 1 g once daily may be underdosed in ICU patients with an increased distribution volume to achieve optimal concentrations in target tissues (3, 11). Our objective was to assess the kinetics of ertapenem in plasma and the interstitial fluid space of skeletal muscle in mechanically ventilated infected ICU patients.

This study was performed in accordance with the Declaration of Helsinki (Edinburgh, Scotland, October 2000) and was approved by the local Ethics Committee. Written informed consent was obtained from a legal representative of each patient. The study was conducted as a single-center open trial. Patients admitted to the polyvalent ICU of Nord University Hospital (Marseille, France) were eligible for inclusion if they met all of the following inclusion criteria: age between 18 and 80 years, mechanical ventilation, diagnosis of ventilator-associated pneumonia (VAP) or intraabdominal infection (IAI) due to a pathogen susceptible to ertapenem (Invanz; Merck Sharp & Dohme Laboratories, Paris, France), and informed consent signed by a relative. Patients with norepinephrine-refractory septic shock, positive hepatitis B virus surface antigen or HIV serology, pregnancy, a history of Clostridium difficile infection, known hypersensitivity to ertapenem, renal impairment (creatinine clearance of ≤30 ml/min/1.73 m² by the Cockroft and Gault formula), or a known contraindication for microdialysis probe insertion were not included. Participants received ertapenem at 1 g · day⁻¹ (over 30 min and for at least 72 h) for management of VAP or IAI.

To determine plasma ertapenem concentrations, arterial blood samples were collected using an indwelling arterial catheter on days 1 and 3 at 15, 40, 65, 120, 240, 420, 780, and 1,380 min after the start of infusion. Plasma was stabilized with a 2-N-morpholinoethanesulfonic acid (MES) solution and frozen until assay. Microdialysis was used to measure free ertapenem in the interstitial fluid. Briefly, a microdialysis probe (CMA60; CMA Microdialysis AB, Stockholm, Sweden) with a molecular mass cutoff of 20 kDa was aseptically inserted into the quadriceps. A physiologic solution was perfused at a rate of 2 µl · min⁻¹ (CMA 107; CMA Microdialysis AB, Stockholm, Sweden). This probe served to sample analytes from the extracellular space by diffusion across a semipermeable membrane. After the onset of ertapenem infusion, microdialysis samples and plasma were collected during the same dosing periods, stabilized with a MES solution, and frozen until assay. For each dialysate, sampling was performed in a specific microvial over 20 min (40 µl). For the pharmacokinetic analysis, we selected the halfway point of each sampling period. The analysis took into account the time necessary for the dialysate to run from the outlet to the microvial. Microdialysis probe calibration for in vivo recovery was performed by the retrodialysis method (2). Briefly, at day 3, the probe was infused with a 500-mg · liter⁻¹ ertapenem solution. After equilibration, microdialysate was sampled for 30 min. In vivo recovery was then calculated as follows: Recovery (%) = [100 − (C_dialysate/ C_perfusate)] × 100. A mean value of 0.55 was used to correct the raw microdialysate data (C_tissue = C_dialysate/0.55).

* Corresponding author. Mailing address: Service d’anesthésie et de réanimation, Hôpital Nord, Chemin des Bourrely, 13915 Marseille Cedex 20, France. Phone: 33491968650. Fax: 33491962818. E-mail: marc.leone@ap-hm.fr.

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Tissue and plasma ertapenem concentrations were measured by a validated high-performance liquid chromatography method with UV detection that was developed in the laboratory. For plasma and microdialysates, the assay was linear over ranges, respectively, of 0.1 to 100 mg·liter⁻¹ and 0.025 to 5 mg·liter⁻¹. It was validated in plasma and normal saline solution. Accuracy and interday variability were less than 15%.

The maximum plasma concentration (C_{max}) and the time to the maximum plasma concentration (T_{max}) were directly observed from the plasma concentration-time curves. Other ertapenem pharmacokinetic parameters were calculated by non-compartmental analysis (WinNonlin 2.1; Pharsight). The area under the plasma concentration-time curve from time zero to infinity (AUC_{0-\infty}) was calculated using the linear trapezoidal rule until the time of the last quantifiable plasma concentration and then extrapolated to infinity by using the quotient of the last measurable concentration to the terminal-phase rate constant (k_{el}), where k_{el} is estimated from the slope of the terminal phase of the logarithmic plasma concentration-time curve using at least three points. The terminal-phase half-life (t_{1/2}) was calculated by the equation t_{1/2} = \ln 2 / k_{el}. The apparent total CL was calculated as dose/AUC_{0-\infty}, and the apparent V was calculated as CL · k_{el}⁻¹.

Two female and five male mechanically ventilated patients (44 ± 19 years old) were included. Five patients were treated for VAP and two for IAI. Norepinephrine was used in three patients for septic shock. The pharmacokinetic parameters of ertapenem in plasma and muscle are shown in Table 1, where data are presented as geometric means ± standard deviations. Estimating the plasma free-ertapenem concentration (about 5%) (9), we found AUC_{tissue}/AUC_{free plasma} ratios of 3.3 ± 2.4 and 2.7 ± 2.4 at days 1 and 3, respectively.

The concentrations of ertapenem in plasma (Fig. 1A) were above those measured in the interstitial fluid (Fig. 1B). Tissue ertapenem concentrations were above the MIC_{90} of the targeted pathogens (Bacteroides fragilis, Enterobacteriaceae) during at least 50% of the dosing period, except in a few individuals (Fig. 2). Norepinephrine did not significantly affect the tissue ertapenem concentrations (data not shown).

The goal of antimicrobial treatment is to eradicate bacteria from infected tissues. For carbapenems, a time above the MIC (T > MIC) of 30 to 40% of the dosing interval has been associated with efficient bactericidal activity (11). In healthy volunteers, a 1-g dose once daily results in muscle tissue drug concentrations higher than the MICs for most of the targeted pathogens for at least 50% of the entire dosing interval (2).

### Table 1. Pharmacokinetic variables for plasma and muscle after a 30-min infusion of ertapenem at a dose of 1 g on days 1 and 3

<table>
<thead>
<tr>
<th>Sample (no. of samples) and day</th>
<th>C_{max} (mg · liter⁻¹)</th>
<th>AUC_{0-\infty} (mg · h · liter⁻¹)</th>
<th>t_{1/2} (h)</th>
<th>V (liters)</th>
<th>CL (liters · h⁻¹)</th>
<th>AUC_{tissue}/AUC_{free plasma} ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma (7)</td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>97 ± 34</td>
<td>390 ± 112</td>
<td>4.6 ± 0.5</td>
<td>16 ± 6</td>
<td>2.5 ± 0.7</td>
<td>NA*</td>
</tr>
<tr>
<td>3</td>
<td>114 ± 39</td>
<td>413 ± 151</td>
<td>4.2 ± 0.6</td>
<td>15 ± 7</td>
<td>2.8 ± 0.9</td>
<td>NA</td>
</tr>
<tr>
<td>Muscle (6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9.3 ± 5.7</td>
<td>44 ± 36</td>
<td>5.0 ± 1.0</td>
<td>NA</td>
<td>NA</td>
<td>0.09 ± 0.05</td>
</tr>
<tr>
<td>3</td>
<td>7.8 ± 4.0</td>
<td>37 ± 17</td>
<td>5.1 ± 2.6</td>
<td>NA</td>
<td>NA</td>
<td>0.09 ± 0.05</td>
</tr>
</tbody>
</table>

*NA, not appropriate.

The same results were reported for skin blister fluid (8). However, the T > MIC thresholds for bactericidal activity are generated using plasma data. Until pharmacodynamic studies are conducted to explore the exposure-response relationships in infected tissue, one should not use plasma exposure thresholds when evaluating tissue drug concentrations.

In our study, the C_{max} values of ertapenem are lower than those reported previously in healthy volunteers (2, 8). The pharmacokinetics of drugs are altered in ICU patients, with a rise in V and CL (12, 14). In the present study, the mean free, non-protein-bound ertapenem concentrations in the intersti-

![FIG. 1. Individual concentrations of ertapenem in plasma (n = 7) (A) and muscle (n = 6) (B) of mechanically ventilated infected patients.](http://aac.asm.org/)
MIC90 values for dose of 1 g (infusion period, 30 min). Horizontal lines (---) indicate MIC values for B. fragilis. The extended-spectrum beta-lactamase-producing Enterobacteriaceae MIC90 is 0.1 mg · liter⁻¹.

FIG. 2. Comparison of ertapenem concentrations in plasma with free-ertapenem concentrations in muscle interstitial fluid of mechanically ventilated infected patients (n = 7) after a single intravenous dose of 1 g (infusion period, 30 min). Horizontal lines (---) indicate MIC values for B. fragilis. The extended-spectrum beta-lactamase-producing Enterobacteriaceae MIC90 is 0.1 mg · liter⁻¹.

Our study has several limitations. The number of patients is relatively small. In addition, protein-unbound ertapenem concentrations were measured in muscle tissue, whereas our patients were treated for VAP and IAI. Thus, the diffusion of ertapenem in infected tissue remains to be explored. However, animal experiments showed that free-imipenem concentrations were similar in lung and muscle tissue (5, 7, 10).

In conclusion, the present study suggests that a 1-g dose of ertapenem is effective in most ICU patients. However, this dose may be insufficient in specific individuals to attain the MICs of targeted bacteria. Our results support the need to assess the clinical efficiency of a 1-g dose in a large population of ICU patients.

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We have no conflict of interest to disclose.

REFERENCES