Diffusion of ertapenem into bone and synovial tissues

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Objectives: The degree of penetration of an antibiotic into the infected site is an important criterion for therapeutic success. Ertapenem is a new carbapenem, exhibiting activity against most Gram-positive and Gram-negative aerobic and anaerobic bacteria commonly recovered from community-acquired infections. However, no studies concerning its diffusion into bone and synovial tissue are available. Our objective was to quantify ertapenem bone and synovial tissue penetration and to compare our data with the MIC90 for causative pathogens.

Patients and methods: In an open-label study, 18 patients who were undergoing elective total hip replacement received a single, parenteral, 1 g dose of ertapenem. One serum, one cortical and cancellous bone and one synovial tissue sample was collected per patient a median [interquartile range (IQR)] of 1.6 (1.5–1.7), 12.4 (11.9–13.1) or 23.8 h (22.6–25.2) later and analysed by HPLC.

Results: The median (IQR) serum concentrations of ertapenem were 70.1 (56.1–75.9), 10.0 (9.1–11.2) and 2.6 mg/L (2.3–3.0), respectively, at the different time points. The median (IQR) cancellous bone tissue concentrations were 13.2 (10.2–14.8), 1.9 (1.7–2.1) and 0.6 µg/g (0.4–0.6) at the different time points, corresponding to a median (IQR) tissue/serum penetration ratio of 0.19 (0.18–0.23). The median (IQR) cortical bone tissue concentrations were 8.0 (6.5–9.5), 1.3 (1.2–1.3) and 0.3 µg/g (0.3–0.4) at the different time points, corresponding to a median (IQR) tissue/serum penetration ratio of 0.13 (0.12–0.14). The median (IQR) synovial tissue concentrations were 26.2 µg/g (22.7–28.4), 4.0 mg/L (3.7–4.4) and 1.0 mg/L (0.9–1.2) at the different time points, corresponding to a median (IQR) tissue/serum penetration ratio of 0.41 (0.39–0.42).

Conclusions: The concentrations after a ertapenem 1 g dose achieved in cancellous and cortical bone tissue and in synovial tissue were greater than the MIC90 for most aerobic organisms for 24 h, and for 12 to 24 h for anaerobic bacteria in healthy volunteers undergoing total hip replacement.

Keywords: diffusion, pharmacokinetics, bone infection

Introduction

The treatment of bone and joint infections remains challenging and a multidisciplinary approach is generally required.1 The degree of penetration of an antibiotic into the infection site is an important criterion for therapeutic success, which is particularly true during the treatment of osteoarticular infections.2 Carbapenems may be used for the treatment of bone and joint mixed infections caused by aerobic and anaerobic microorganisms.3 Ertapenem is a new carbapenem, exhibiting activity against most Gram-positive (including oxacillin-susceptible Staphylococcus aureus) and Gram-negative aerobic and anaerobic bacteria commonly recovered from community-acquired infections.3 Although the pharmacokinetic and pharmacodynamic profile of ertapenem has been widely described in vitro and in vivo, no data concerning its penetration into bone and synovial tissues are available.3-7

In the present study, we examined the cortical and cancellous bone tissue and the synovial tissue penetration of ertapenem after a single, intravenous dose of 1 g administered to volunteers undergoing total hip replacement surgery. The results were compared with the MIC90 for susceptible microorganisms in order to evaluate the potential role of ertapenem in the treatment of bone and joint infections.

Materials and methods

Patients

This was a single-dose, open-label, single-arm, non-comparative study. The protocol was approved by the local Ethics Committee and written informed consent was obtained from all the patients. Adult patients who were undergoing total hip replacement surgery were

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enrolled. Patients were excluded if they were allergic to β-lactam antibiotics, were receiving any other antimicrobial therapy or exhibited diabetes, angiopathy or renal dysfunction, defined as creatinine clearance <40 mL/min or a serum creatinine concentration >200 μmol/L.

**Drug administration and sample collection**

Patients received ertapenem 1 g as a single intravenous 30 min infusion 24, 12 or 1 h before surgery, then cefazolin 2 g as standard intravenous perioperative prophylaxis at the time of induction of anaesthesia. Total hip replacement surgery involved resection of the femoral bone (which consists of cancellous and cortical bone tissue) and synovial tissue, followed by implantation of the prosthetic hip joint.

Each patient underwent one blood and one bone and synovial tissue sampling. Blood samples were collected at the time of femoral bone and synovial tissue resection. All bone and synovial samples were taken from uninfected tissue. The exact time of sample removal after the beginning of ertapenem infusion was recorded and bone and synovial tissue samples were stored at −80°C until they were analysed.

**Sample preparation and analytical procedures**

Cancellous bone fragments were deep frozen in liquid nitrogen on the day of sample preparation then crushed into small pieces, and cortical bone tissues were dissected into small pieces. All bone samples were prepared as follows. Two hundred milligrams of tissue sample was incubated for 15 min in 2 mL of homogenizing reagent (water/methanol/perchloric acid/orthophosphoric acid, 500:500:10:1) and homogenized for 1 min using a vortex. To ensure complete extraction of ertapenem, the homogenized samples were stored overnight at 4°C.

All samples [calibration standards, quality controls (QCs) or clinical] were thawed at room temperature. In a haemolysis tube, 200 μL of sample was mixed with 350 μL of imipenem at a concentration of 25 mg/L in NaH2PO4, pH 4, 40 mM buffer. The solution of imipenem was prepared just before analysis and was stable for 12 h at room temperature. A 400 μL aliquot was transferred into a Microcon YM10 (Millipore, Bedford, USA) centrifugal device, which was centrifuged at 12,000 rpm at room temperature for 20 min in the sigma model 2MK centrifuge. A 125 μL aliquot of the filtrate was transferred into an autosampler vial and 40 μL was injected into the chromatographic system. All of these operations were performed at room temperature.

Stability of ertapenem in plasma and in cancellous and cortical bone tissue filtrates was evaluated after short-term storage (24 h) at room temperature and at 4°C. The stability of stock solutions of ertapenem and imipenem was assessed at room temperature for 24 h. The long-term storage stability of ertapenem was evaluated for serum and cancellous and cortical bone tissue at −80°C. These QC were analysed at 3 and 6 months.

Recovery of ertapenem was evaluated by comparing the mean peak areas of the different ultrafiltrated QC samples with those prepared by adding compounds to ultrafiltrate plasma and cancellous and cortical bone tissue blanks at corresponding concentrations. The variability of recovery results was determined.

The concentrations of free ertapenem were determined by an HPLC method previously developed in our laboratory. The HPLC method was used with ultraviolet detection set at a wavelength of 305 nm (bandwidth of 4 and chromatographic run time of 14 min) and separation on a Prontosil AQ C18 column, with imipenem used as internal standard. This assay was linear over the concentration range of 0.5–100 mg/L in serum. Limits of detection and quantification were, respectively, 0.05 and 0.25 mg/L. Validation data for accuracy and precision were CV <2.48% and 8.25%, accuracy in the range 98.1% to 104.2% and 102.2% to 108.4%, respectively, for intra- and inter-day.

**Results**

Eighteen patients completed the study (Table 1). Ertapenem was well tolerated by all patients. Individual ertapenem concentrations appear in Table 2, showing a median (IQR) tissue/serum penetration ratio of 0.19 (0.18–0.23), 0.13 (0.12–0.14) and 0.41 (0.39–0.42), respectively, for cancellous bone, cortical bone and synovial tissues.

Long-term stability studies showed no significant degradation of QC samples stored at −80°C and analysed at 3 and 6 months. No endogenous substance interfered with imipenem and ertapenem in blank plasma and cancellous and cortical bone tissues. Stock solutions of ertapenem and imipenem in buffer showed no perceptible degradation between solutions kept at room temperature for 24 h and freshly prepared solutions. Mean ertapenem concentrations ranged from 96.9% to 102.8% for plasma, from 91.2% to 100.8% for cancellous bone tissue and from 90.6% to 98.6% for cortical bone tissue compared with freshly prepared QCs. Ultrafiltrates were stable (>90%) for 24 h at room temperature and at 4°C.

**Discussion**

The efficacy of ertapenem in adults with complicated bacterial infections has been examined in large well-designed trials in the following five indications: complicated intra-abdominal infection, complicated skin and skin structure infection, community-acquired pneumonia, acute pelvic infection and complicated urinary tract infection. In addition, ertapenem has recently shown similar efficacy to piperacillin/tazobactam in the treatment of diabetic foot infection. However, no data concerning the use of ertapenem in bone and joint infections are available, although this agent exhibits a wide spectrum of activity against pathogens frequently involved, such as oxacillin-susceptible *S. aureus*, *Staphylococcus epidermidis*, various streptococci, Enterobacteriaceae and anaerobes, with the exception of oxacillin-resistant *S. aureus* and *Pseudomonas aeruginosa*. This is the first study evaluating the diffusion of ertapenem into bone and synovial tissues. Our study shows that after the administration of ertapenem 1 g intravenously to uninfected patients, the concentrations achieved in cancellous and cortical bone and synovial tissues are above the ertapenem MIC90 for most Enterobacteriaceae and oxacillin-susceptible *S. aureus* (0.25–0.5 mg/L) for 24 h, and 12–24 h for anaerobes.
Table 2. Individual ertapenem serum and tissue concentrations and serum/tissue concentration ratios

<table>
<thead>
<tr>
<th>Patient</th>
<th>Exact time of sample removala (h)</th>
<th>Ertapenem serum concentration (mg/L)</th>
<th>Ertapenem tissue concentration (μg/g)</th>
<th>Tissue/serum ratio of ertapenem concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>77.2</td>
<td>12.1</td>
<td>0.16</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>47.7</td>
<td>9.6</td>
<td>0.20</td>
</tr>
<tr>
<td>3</td>
<td>1.8</td>
<td>76.0</td>
<td>14.2</td>
<td>0.19</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>53.2</td>
<td>8.9</td>
<td>0.17</td>
</tr>
<tr>
<td>5</td>
<td>1.6</td>
<td>64.8</td>
<td>15.0</td>
<td>0.23</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>75.4</td>
<td>18.1</td>
<td>0.24</td>
</tr>
<tr>
<td>7</td>
<td>11.8</td>
<td>8.7</td>
<td>2.0</td>
<td>0.23</td>
</tr>
<tr>
<td>8</td>
<td>10.9</td>
<td>12.4</td>
<td>2.7</td>
<td>0.22</td>
</tr>
<tr>
<td>9</td>
<td>12.5</td>
<td>9.3</td>
<td>1.3</td>
<td>0.14</td>
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<tr>
<td>10</td>
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<td>12.3</td>
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<td>14.0</td>
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<tr>
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<tr>
<td>14</td>
<td>24.1</td>
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<tr>
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<tr>
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<td>0.23</td>
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<tr>
<td>17</td>
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<td>0.5</td>
<td>0.16</td>
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<tr>
<td>18</td>
<td>21.4</td>
<td>2.4</td>
<td>0.6</td>
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<td>Median</td>
<td>—</td>
<td>70.1</td>
<td>13.2</td>
<td>0.19</td>
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<tr>
<td>IQR</td>
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<td>10.2–14.8</td>
<td>0.18–0.23</td>
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</table>

aAfter the start of ertapenem infusion.
The findings from our study suggest that ertapenem levels in cancellous and cortical bone tissue and in synovial tissue after a single daily dose of 1 g should be efficient against most of the aerobic susceptible microorganisms usually encountered in osteoarticular infections, but that higher daily doses might be required in case of anaerobic bacteria.

Nevertheless, the major limit of our study is that it was performed using non-infected bone and synovial tissue samples; hence it would be hazardous to extrapolate the results to concentrations achieved in infected osteoarticular tissues, in which the disposition of antibiotics might be very different. Moreover, the few patients included in the current study were old with moderate degree of renal impairment and hypoalbuminaemia, and it is possible that this might not be a very representative sample, from the physiopathological and pharmacokinetic points of view, of what could be considered an adult population.

However, our results provide the basis for performing clinical trials assessing the role of ertapenem in the treatment of bone and joint infections. Ertapenem exhibits moderate bone tissue penetration of 10% to 20% and synovial tissue penetration of ~40%. However, the ertapenem concentrations achieved in synovial, and cancellous and cortical bone uninfected tissues of our study population were above the MIC90s for most aerobic pathogens generally encountered in bone and joint infections for 100% of a notional 24 h dosing interval and 50% to 100% of this interval for anaerobic bacteria. These results suggest that ertapenem could be used as antimicrobial prophylaxis during hip surgery. However, given the availability of narrower-spectrum and less expensive antimicrobial agents, ertapenem may not be recommended as first-line therapy. Moreover, further clinical studies are required to evaluate the efficacy of ertapenem in the treatment of osteoarticular infections.

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Transparency declarations

None to declare.

References