Clinical pharmacokinetics of meropenem after the first and tenth intramuscular administration

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We investigated the pharmacokinetics of meropenem after the first and tenth im administration in patients with respiratory tract infections. Ten patients (mean age 63.8 ± 5.2 years) received meropenem 500 mg tds for at least ten doses, and plasma and urine antibiotic concentrations were determined by microbiological assay. After the first injection a mean peak plasma concentration of 7.93 ± 1.29 mg/L was observed at 1 h. Trough levels at 8 h (0.29 ± 0.16 mg/L) were detectable in five of ten treated patients. The mean terminal half-life was 1.08 ± 0.2 h with an area under the curve (AUC) value of 23.8 ± 4.59 mg/L.h, and a cumulative urinary recovery at 8 h of 48.43 ± 3.12%. There was no evidence of change in the pharmacokinetics of meropenem after repeated im administration, though the mean peak plasma concentration and AUC value were slightly increased. The accumulation ratio (assessed using AUC values) was 1.18 ± 0.19 after multiple doses and was considered to be of little kinetic and clinical importance. Moreover, many of the trough concentrations of meropenem were below the limit of detection of the assay. After im administration meropenem concentrations exceeded 0.5 mg/L for longer than previously described following iv infusion. No adverse events were reported.

Introduction

Meropenem, a new carbapenem, differs from imipenem in having a side chain at C2 which assures it a broad spectrum of activity against aerobes and anaerobes, including β-lactamase producing pathogens and Pseudomonas aeruginosa (Jones et al., 1989; Neu, Novelli & Chin, 1989). The β-methyl substitution at C1 on the carbapenem nucleus reduces the ability of dehydropeptidase I (DHP-I) to attack the β-lactam molecule. Meropenem is thus a poor substrate of human renal DHP-I and does not require co-administration with a DHP-I inhibitor such as cilastatin (Fukasawa et al., 1992). Unlike imipenem, when administered alone meropenem appears to be well tolerated by the kidney (Birnbaum et al., 1985; Topham et al., 1989).

The pharmacokinetics of meropenem have been studied in young and elderly healthy volunteers and in patients with various degrees of renal function after iv infusion (Bax et al., 1989; Christesson et al., 1992; Leroy et al., 1992; Ljungberg & Nilsson Ehle, 1992; Chimata et al., 1993). This carbapenem derivative has a pharmacokinetic profile very similar to that of imipenem when given with cilastatin, and a significant linear
relationship between total body clearance and creatinine clearance has been observed, with reduction in the renal excretion rate related to age or renal impairment (Nilsson Ehle et al., 1991; Christensson et al., 1992). Since there are no published data on the pharmacokinetics of meropenem following im administration, we investigated the profile of this drug following the first and tenth im administration of 500 mg doses in patients suffering from respiratory tract infections.

Materials and methods

Study design

This was a single centre, open study of the pharmacokinetics of im meropenem 500 mg tds given for a minimum of ten doses. Meropenem mixed with sodium carbonate (1:0.75 molar ratio) was supplied by Zeneca S.p.A. (Milan, Italy) in vials containing 500 mg of active drug as the trihydrate. The antibiotic powder was reconstituted with 2 mL of sterile 0.164 M sodium carbonate.

Subjects

Eleven patients with respiratory tract infections were studied. None of the patients had a history of hypersensitivity to β-lactams. Nine of the ten male patients had chronic obstructive pulmonary disease (COPD) with bronchitis, the remaining patient had bronchitis alone. The single female recruited into the study had bronchiectasis. All infections were of mild or moderate severity. One male patient was ineligible for analysis because of unrecorded alternative antibiotic administration within 3 days before study entry, and therefore ten patients were assessed. Patient characteristics are given in Table I, but notably all individuals had normal renal and hepatic function for their age. Creatinine clearance (\( C_{\text{cr}} \)) was calculated with the formulas \( 88 \times (145 \text{-age in years}) - 3/ \text{serum creatinine concentration in micromoles per litre} \) and \( 75 \times (145 \text{-age in years}) - 3/ \text{serum creatinine concentration in micromoles per litre} \) for male and female patients, respectively (Christensson et al., 1992). Written informed or witnessed verbal consent for study entry was obtained from all subjects.

Blood and urine samples

Heparinised venous blood samples were obtained before administration and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6 and 8 h after the first and tenth doses. Blood samples were centrifuged immediately after collection. Urine was collected at 0-2, 2-4, 4-6 and 6-8 h after the first and tenth doses. Plasma and urine samples were rapidly frozen in an ethanol/dry-ice mixture and then stored at \(-80^\circ \text{C}\) until assayed.

Assay

Meropenem concentrations in plasma and urine were determined in triplicate by a standard large-plate agar diffusion technique, using Nutrient Agar (Difco) and Escherichia coli NIHJ (National Institute of Health, Japan) as the test organism with a lower limit of sensitivity of 0.125 mg/L. Standard concentrations were prepared daily in pooled plasma for blood samples, and in 0.05 M phosphate buffer pH 7.0 for urine
assays. Best fit standard curves were obtained by linear regression analysis. The linearity between 0.125 and 32 mg/L was log $y = 0.107x - 2.24$ for plasma and log $y = 0.142x - 2.72$ for urine samples, with a correlation coefficient $\geq 0.998$. For all samples the intra-assay coefficients of variation ranged from 5.7 to 9.5%; the inter-assay coefficients of variation for the 0.5 mg/L standards ranged from 6.2 to 6.5%.

**Pharmacokinetics analysis**

The nominal 500 mg dose of meropenem was used in the calculation of derived parameters. The pharmacokinetic analysis was performed with a computerised program (Siphar, version 4.0; Simed, Créteil, France) using weighted least squares regression. The data were fitted by a first order input to a single compartment model using an appropriate weighting $1/y$. The maximum plasma concentration ($C_{max}$) and the time to reach the peak ($T_{max}$) were determined from the plasma-concentration-time data. The absorption half-life ($T_{abs}$) and terminal half-life ($T_{1/2}$) were calculated from the rate constants of the fitted model. The area under the concentration-time curve (AUC) was determined by trapezoidal rule and extrapolated to infinity. The plasma clearance ($Cl$) and volume of distribution at steady state ($V_{dss}$) were calculated by conventional methods assuming complete bioavailability (Gibaldi & Perrier, 1982). The urinary recovery of meropenem ($fu$) 8 h after administration was expressed as a percentage of the nominal dose.

**Statistical analysis**

Statistical analysis to compare data for the first and the tenth dose was performed using analysis of variance. For AUC and peak plasma levels the model was fitted to the log transformed data.

**Results**

The mean peak plasma concentration of meropenem after the first injection (7.9 ± 1.3 mg/L) was observed at 1 h (Figure), with a mean absorption half-life ($T_{abs}$) of 0.53 ± 0.14 h (Table II). The antibiotic was still detectable in five of the ten patients at 8 h, regardless of their age or $Cl_{r}$, with a mean concentration of 0.3 ± 0.2 mg/L. The mean plasma concentration time curve obtained after the tenth dose was similar to that observed after the first injection, with a mean peak plasma level of 9.5 ± 3.1 mg/L, 1 h after the tenth dose (Figure). Mean antibiotic trough concentrations ranged from 0.4 ± 0.1–0.3 ± 0.2 mg/L before the tenth and eleventh administrations, respectively. Detectable antibiotic before the tenth and the eleventh dose was observed in seven and four patients, respectively. In the other cases values were below the lower limit of sensitivity. Other pharmacokinetic parameters of meropenem are given in Table II. The extent of accumulation was assessed using ratios of AUC (accumulation ratio = 1.18 ± 0.19) and $C_{max}$ ($C_{max}$ ratio = 1.26 ± 0.44) after the two doses. Both showed a small increase which was statistically significant ($P = 0.011$) for the AUC ratio but not for the $C_{max}$ ratio ($P = 0.146$). Meropenem urinary concentrations were high and sufficient to inhibit most susceptible pathogens in the 8 h period following im administration. No significant differences were observed among urinary concentrations after the first or tenth dose even after 6–8 h ($P = 0.052$) (Table III). The cumulative
**Table I.** Characteristics of the ten patients who completed the study

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>Total bilirubin (μmol/L)</th>
<th>Alkaline phosphatase (IU/L)</th>
<th>AST* (IU/L)</th>
<th>ALT* (IU/L)</th>
<th>UREA (mmol/L)</th>
<th>Serum creatinine (μmol/L)</th>
<th>Creatinine clearance (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± S.D.</td>
<td>63.8 ± 5.2</td>
<td>62.8 ± 11.1</td>
<td>1.66 ± 0.04</td>
<td>10.4 ± 3.4</td>
<td>135.1 ± 25.7</td>
<td>19.1 ± 8.9</td>
<td>21.8 ± 10.1</td>
<td>5.8 ± 2.1</td>
<td>92.8 ± 8.8</td>
<td>74.1 ± 10.6</td>
</tr>
<tr>
<td>Range</td>
<td>56–72</td>
<td>48–85</td>
<td>16.1–1.72</td>
<td>5.1–15.4</td>
<td>85–168</td>
<td>10–38</td>
<td>12–40</td>
<td>2.8–10.8</td>
<td>79.6–114.9</td>
<td>56.2–94.8</td>
</tr>
</tbody>
</table>

*AST, Aspartate aminotransferase.
*ALT, Alanine aminotransferase.

**Table II.** Pharmacokinetics of meropenem in plasma after the first and tenth im doses of 500 mg in ten patients (mean ± S.D.)

<table>
<thead>
<tr>
<th></th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (mg/L·h)</th>
<th>V&lt;sub&gt;d&lt;/sub&gt; (L)</th>
<th>CI (mL/min)</th>
<th>K&lt;sub&gt;e&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>K&lt;sub&gt;d&lt;/sub&gt; (h&lt;sup&gt;-1&lt;/sup&gt;)</th>
<th>f&lt;sub&gt;uni&lt;/sub&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st dose</td>
<td>8.3 ± 2.0</td>
<td>1.1 ± 0.3</td>
<td>0.53 ± 0.14</td>
<td>23.8 ± 4.6</td>
<td>19.7 ± 2.4</td>
<td>268.0 ± 31.8</td>
<td>1.5 ± 0.5</td>
<td>0.7 ± 0.1</td>
<td>48.4 ± 3.1</td>
</tr>
<tr>
<td>10th dose</td>
<td>10.2 ± 3.5</td>
<td>1.15 ± 0.37</td>
<td>0.46 ± 0.12</td>
<td>27.9 ± 6.7</td>
<td>19.0 ± 2.4</td>
<td>276.0 ± 28.7</td>
<td>1.6 ± 0.4</td>
<td>0.7 ± 0.1</td>
<td>51.2 ± 5.4</td>
</tr>
</tbody>
</table>

*Computed value (the actual maximum concentration was achieved in some patients after the 1 h assay).
*Calculated assuring complete bioavailability
urinary recovery following the tenth dose was significantly higher than after the first dose \((P = 0.025)\), though this difference of 2.8% of the dose is small and was not considered of any clinical significance (Table II). Meropenem exceeded the concentrations of 2.0 and 0.5 mg/L after a 500 mg dose for approximately 4.3 and 7.0 h, respectively. No clinically significant effects were observed in standard haematology, biochemistry or urinalysis tests performed before the first or last doses. No symptoms or adverse events were reported.

**Discussion**

Pharmacokinetic parameters of meropenem were determined for a nominal dose of 500 mg, and assuming complete bioavailability. Recently, T. L. Hunt (Zeneca data on file–1994) determined the pharmacokinetics of meropenem after a single im 500 mg dose in comparison to iv administration in 24 young healthy volunteers, and found 93.8% bioavailability with the im dose. Therefore, in the present study, when considering this fraction of the dose absorbed, a difference of about 10% in results should be estimated for plasma clearance and volume of distribution values, instead of assuming 100% bioavailability.

The plasma concentrations of meropenem after multiple doses in our study were slightly higher than those after the first dose. However, the extent of accumulation, as assessed by AUC and \(C_{\text{max}}\), was rather small (<30% increases) and was of little pharmacokinetic and clinical importance. Many of the trough concentrations of

**Table III. Urinary concentrations of meropenem (mg/L) following the first and tenth im dose (500 mg) in ten patients (mean ± s.d.)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>0–2</th>
<th>2–4</th>
<th>4–6</th>
<th>6–8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>328.4 ± 114.7</td>
<td>553.1 ± 243.2</td>
<td>198.6 ± 115.8</td>
<td>57.5 ± 44.5</td>
</tr>
<tr>
<td>10th</td>
<td>355.6 ± 175.3</td>
<td>726.7 ± 300.4</td>
<td>276.2 ± 175.5</td>
<td>97.4 ± 74.3</td>
</tr>
</tbody>
</table>
meropenem were below the limit of assay detection after both doses, without any relation to the patients' characteristics such as age or Cl_a values, which meant that a minimum plasma concentration ratio could not be calculated. This indicates that there was no significant accumulation of the antibiotic. The urinary recovery of meropenem was slightly higher after the tenth dose, which is consistent with the increased plasma concentrations. The pharmacokinetic parameters derived after the first and tenth doses were very similar. Our results parallel those observed by other authors after iv administration of meropenem (Bax et al., 1989; Nilsson Ehle et al., 1991; Leroy et al., 1992; Liungberg & Nilsson Ehle, 1992).

Following im administration we observed meropenem plasma concentrations greater than the MICs for most pathogens for longer than after iv infusion. For example, the time after im injection when meropenem concentrations exceeded 2.0 and 0.5 mg/L was 4.3 and 7.0 h, respectively; the corresponding times following iv administration were 2.7 and 4.9 h, respectively (Bax et al., 1989). Moreover, plasma concentrations exceeded 0.25 mg/L for at least 7 h (i.e. the MIC_90 for enterobacteria and methicillin-sensitive staphylococci (Jones et al., 1989; Neu et al., 1989)). In a previous study of the iv administration of meropenem, Ljungberg & Nilsson Ehle (1992) found that the clearance in elderly subjects was reduced according to the decline in renal function with age, as measured by Cl_a. Our study shows that the use of a 500 mg im dose of meropenem is appropriate in patients with calculated Cl_a ≥ 55 mL/min.

In conclusion, meropenem, after multiple im doses of 500 mg, exhibited almost the same kinetic parameters as after a single dose. No pharmacokinetically significant accumulation was observed after four days of treatment (500 mg tds). Finally, in a modestly elderly group of patients we observed no side effects, thus indicating the potential safety of administering the antibiotic thrice daily.

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References


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