Peritoneal penetration of doripenem after intravenous administration in abdominal-surgery patients

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Received 22 May 2007; returned 4 August 2007; revised 30 August 2007; accepted 31 August 2007

Objectives: This study aimed to examine the peritoneal penetration of intravenous doripenem, a novel carbapenem used for the treatment of intra-abdominal infections.

Patients and methods: Doripenem (500 mg) was administered to 10 patients before abdominal surgery. Venous blood and peritoneal exudate samples were obtained at the end of infusion (0.5 h) and every hour for 6 h afterwards. The drug concentrations in serum and exudate were measured using HPLC, estimated by non-compartmental pharmacokinetic analysis and fitted to a three-compartment pharmacokinetic model in order to assess the exposure time that the drug concentration remained above MIC.

Results: The AUC0–∞ was 59.3 ± 7.2 mg·h/L (mean ± SD) in serum and 49.3 ± 6.5 mg·h/L in exudate, and the exudate/serum ratio was 0.84 ± 0.13. The observed maximum concentration was 46.9 ± 7.4 mg/L at 0.5 h in serum and 24.5 ± 6.5 mg/L at 0.7 ± 0.4 h in exudate, and the exudate/serum ratio was 0.53 ± 0.17. The compartmental analysis showed that the average concentrations remained higher in exudate than in serum after 0.81 h post-dose, and the average drug-exposure times in serum (91% fraction unbound) and exudate were: 73.6% and 78.2% at an MIC of 1 mg/L; 37.0% and 41.5% at 4 mg/L; and 12.7% and 13.1% at 16 mg/L.

Conclusions: Following intravenous administration, doripenem penetrated well into peritoneal exudate of abdominal-surgery patients, and the drug-exposure times in exudate were greater than or equal to those estimated from serum data.

Keywords: pharmacokinetics, peritoneal exudate, carbapenems

Introduction

Doripenem is a novel parenteral carbapenem with a broad spectrum of activity against Gram-positive and Gram-negative aerobic and anaerobic bacteria. It has been used, clinically in Japan and investigationally in the USA, for the treatment of intra-abdominal infections and also for antibacterial prophylaxis in abdominal surgery.1,2 Doripenem must act at the site of infection, and the drug’s penetration into an intra-abdominal site, such as peritoneal exudate and ascitic fluid, would be an important factor of its efficacy. However, the doripenem concentrations in peritoneal fluid have not been described to date.

The objective of this study was therefore to examine the peritoneal pharmacokinetics of doripenem after intravenous administration. In this study, patients who underwent abdominal surgery for the relief of inflammatory bowel disease were chosen as the study subjects because they have a sufficient amount of peritoneal exudate for sampling. A non-compartmental pharmacokinetic analysis was performed to estimate the rate and extent of doripenem penetration from the systemic circulation into peritoneal exudate. Compartmental pharmacokinetic modelling was employed to accurately assess the cumulative percentage of a 24 h period that the drug concentration exceeds the MIC under steady-state pharmacokinetic conditions (T > MIC),3 because doripenem exhibits a
time-dependent *in vitro* activity and the antibacterial effects in animals closely correlate with $T > \text{MIC}$.

**Patients and methods**

This prospective study was conducted at the Hiroshima University Hospital. The study protocol and informed consent form were reviewed and approved by the Ethics Committee of the institution.

Abdominal-surgery patients for treatment of ulcerative colitis or Crohn's disease who met the following criteria were included in the study: patients of both sexes over 20 years of age, patients who were preferable to antibacterial prophylaxis for laparotomy, and patients willing and able to provide their written informed consent. Patients who were pregnant and hypersensitive to carbapenems were excluded.

Five hundred milligrams of doripenem (FINIBAX; Shionogi & Co., Ltd, Osaka, Japan) was administered by 0.5 h infusion before abdominal surgery and given post-operatively at 8 h intervals (500 mg every 8 h for 2 days). Venous blood and peritoneal exudate samples (3 mL) were obtained at the end of the first infusion and 1, 2, 3, 4, 5 and 6 h afterwards. The exudate in the abdominal cavity was collected manually with a syringe during surgery and was taken post-operatively through an intra-abdominal drain. The samples were immediately placed in polypropylene tubes on ice and centrifuged at 3000 g for 10 min, and 20 mL of the centrifuged solution was injected onto a chromatograph. Chromatography was carried out using a reversed-phase column [XBridge C18 5 μm; Waters Corporation, Milford, MA, USA] and ultraviolet absorbance detection was at 254 nm and stored at -40℃ within 0.5 h after sampling. All samples were analysed within 3 days of collection.

The total concentrations of doripenem in serum and peritoneal exudate were determined using HPLC. Serum and exudate samples (400 μL) were transferred to an ultrafiltration device (Nanosep 10K; Pall Corporation, Northborough, MA, USA). The device was centrifuged at 12 000 g for 10 min, and 20 μL of the filtrated solution was injected onto a chromatograph. Chromatography was carried out using a reversed-phase column [XBridge C18 5 μm (4.6 × 150 mm); Waters Corporation, Milford, MA, USA] and ultraviolet absorbance was detected at 300 nm. A mixture of 0.1 M sodium acetate buffer (pH 4.6) and acetonitrile (95:5, v/v) was used as a mobile phase at a flow rate of 1 mL/min. The column temperature was 40℃, and the retention time for doripenem was 5.9 min. The method was linear over a concentration range of 0.05—100 mg/mL and the lower limit of quantification was 0.05 mg/mL in both serum and exudate. The precisions in intra- and inter-day assay (n = 5) were within 1.8% and 3.7%, respectively. The accuracies in the intra- and inter-day assay were 99.8% to 105.2% and 99.0% to 102.8%, respectively.

Non-compartmental and compartmental pharmacokinetic analyses were performed using the MULTI program. The AUC$_{0-\infty}$ and mean residence time (MRT) were calculated based on the trapezoidal rule. The total clearance (CL$_{tot}$) was estimated as dose (500 mg)/AUC$_{0-\infty}$, and V$_{ss}$ was calculated as CL$_{tot} \times$ MRT. C$_{max}$ was the observed maximum concentration of doripenem, and T$_{max}$ was the time to C$_{max}$.

A three-compartment model (1, central; 2, peripheral; 3, peritoneal) was used to fit the drug concentrations in serum and peritoneal exudate, because it described the current data set better than a two-compartment model (1, central; 2, peritoneal). In the three-compartment model equations, V$_1$ and V$_3$ are the volumes of distribution of the central and peritoneal compartments; $k_{21}$, $k_{12}$ and $k_{31}$ are the first-order transfer rate constants connecting the compartments; and $\alpha$, $\beta$ and $\gamma$ are the macro rate constants. With these parameter estimates, free $T > \text{MIC}$ ($fT > \text{MIC}$) in serum and $T > \text{MIC}$ in exudate were predicted as follows; the time point at which the simulated concentration (91% fraction unbound in serum; FINIBAX package insert) coincided with a specific MIC value (1, 4 or 16 mg/L) was determined, and the duration for which the drug concentration remained at the MIC was calculated as the cumulative percentage of a 24 h period.

A statistical analysis was performed using the SPSS software (version 15.0J; SPSS Japan Inc., Tokyo). The Wilcoxon matched-pairs signed-ranks test was used as appropriate to determine differences in drug-exposure times between the two sites; $P < 0.05$ (two-tailed) was considered statistically significant.

**Results and discussion**

Ten abdominal-surgery patients (eight men and two women) participated in the study. The demographics were: age, 36.7 ± 9.5 years (mean ± SD); weight, 54.3 ± 14.9 kg; serum creatinine clearance, 96.4 ± 20.4 mL/min; and blood-urea nitrogen, 3.82 ± 1.24 mmol/L. No patient had been infected or had received antibacterial therapy for at least 14 days before the study.

The non-compartmental pharmacokinetic parameters of doripenem are summarized in Table 1. The AUC$_{0-\infty}$ was 59.3 ± 7.2 mg.h/L in serum and 49.3 ± 6.5 mg.h/L in peritoneal exudate, and the AUC$_{0-\infty}$ ratio of exudate to serum (commonly used as the index of peritoneal penetration) was 0.84 ± 0.13. The observed maximum concentration was 46.9 ± 7.4 mg/L at 0.5 h in serum and 24.5 ± 6.5 mg/L at 0.7 ± 0.4 h in exudate, and the exudate/skin ratio was 0.53 ± 0.17. V$_{ss}$ and CL$_{tot}$ were 11.0 ± 1.7 L and 8.56 ± 1.14 L/h, respectively.

The three-compartmental parameters were: V$_1$, 7.53 ± 1.79 L; V$_3$, 5.25 ± 1.95 L; $k_{21}$, 0.719 ± 0.167 1/h; $k_{12}$, 1.81 ± 0.97 1/h; and $k_{31}$, 2.87 ± 1.07 1/h. The $\alpha$, $\beta$ and $\gamma$ half-lives were 0.221 ± 0.107, 0.370 ± 0.089 and 1.62 ± 0.34 h, respectively. The simulation curves using the mean estimates were fitted well to the measurements in serum and peritoneal exudate (Figure 1) and showed that the average concentrations remained higher in exudate than in serum after 0.81 h post-dose. At MICs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD (range)</th>
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<tbody>
<tr>
<td><strong>Serum</strong></td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (mg.h/L)</td>
<td>59.3 ± 7.2 (47.0—70.7)</td>
</tr>
<tr>
<td>C$_{max}$ (mg/L)</td>
<td>46.9 ± 7.4 (36.9—59.9)</td>
</tr>
<tr>
<td>T$_{max}$ (h)</td>
<td>0.5</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>1.29 ± 0.16 (1.17—1.68)</td>
</tr>
<tr>
<td>V$_{ss}$ (L)</td>
<td>11.0 ± 1.7 (8.5—13.7)</td>
</tr>
<tr>
<td>CL$_{tot}$ (L/h)</td>
<td>8.56 ± 1.14 (7.07—10.6)</td>
</tr>
<tr>
<td><strong>Peritoneal exudate</strong></td>
<td></td>
</tr>
<tr>
<td>AUC$_{0-\infty}$ (mg.h/L)</td>
<td>49.3 ± 6.5 (40.7—61.2)</td>
</tr>
<tr>
<td>C$_{max}$ (mg/L)</td>
<td>24.5 ± 6.5 (16.4—34.7)</td>
</tr>
<tr>
<td>T$_{max}$ (h)</td>
<td>0.7 ± 0.4 (0.5—1.5)</td>
</tr>
<tr>
<td>AUC$<em>{0-\infty}$, exudate/AUC$</em>{0-\infty}$, serum</td>
<td>0.84 ± 0.13 (0.70—1.07)</td>
</tr>
<tr>
<td>C$<em>{max}$, exudate/C$</em>{max}$, serum</td>
<td>0.53 ± 0.17 (0.33—0.85)</td>
</tr>
</tbody>
</table>
Peritoneal penetration of doripenem

Figure 1. Observed concentrations and simulation curves in serum (filled circles, continuous line) and peritoneal exudate (open circles, broken line) after a single 0.5 h of infusion of 500 mg of doripenem (mean ± SD, n = 10). The simulation curves were illustrated using the mean three-compartmental parameter estimates.

of 1, 4 and 16 mg/L, $fT > MIC$ in serum were $73.6 \pm 12.0\%$ (range 60.9% to 97.6%), 37.0 ± 6.3% (28.1% to 48.2%) and 12.7 ± 1.7% (10.1% to 15.7%); and $T > MIC$ in exudate were $78.2 \pm 10.6\%$ (63.4% to 99.7%), 41.5 ± 7.3% (33.6% to 58.3%) and 13.1 ± 4.0% (5.0% to 18.5%), respectively. The values were slightly greater for exudate than for serum, and the differences were statistically significant at MICs of 1 and 4 mg/L but not at an MIC of 16 mg/L.

Interestingly, $C_{max}$ for peritoneal exudate was approximately half of the value for serum; on the contrary, the drug-exposure time in exudate was greater than or equal to the value for serum. We presume this because the difference in $T_{max}$ for the two sites was short with an average time of 0.2 h, and the concentrations were considered to remain higher in exudate than in serum after 0.81 h post-dose. This pharmacokinetic property of doripenem may come from a comparatively low molecular weight (438.5) and protein binding (9%).

The average times above MIC for 1 and 4 mg/L in peritoneal exudate were 78.2% and 41.5%, respectively. The in vitro activities (MIC$_{90}$) of doripenem against clinical isolates of *Escherichia coli*, *Streptococcus* species and *Bacteroides* species, the most common pathogens that cause intra-abdominal infections, have been reported to be 0.03, 0.5 and 2 mg/L, respectively.7,8 Meanwhile, the $T > MIC$ target value required for bactericidal effect of doripenem is, like other carbapenems, considered to be $\sim 40\%$ of the dosing interval.9,10 Therefore, an empirical regimen of 500 mg every 8 h was indicated to provide sufficient bactericidal exposure in the abdominal cavity.

This study has a limitation in that the subjects were uninfected patients. In order to confirm the therapeutic significance of our pharmacokinetic results and to optimize the dosing regimen for the treatment of intra-abdominal infections, we need clinical studies in infected patients investigating the relationship between the peritoneal penetration and exposure of doripenem and the therapeutic efficacy.

In conclusion, the present study has demonstrated that intravenous doripenem penetrated into peritoneal exudate of abdominal-surgery patients rapidly and extensively, and the drug-exposure times in exudate were greater than or equal to those estimated from serum data. These results expand our knowledge of doripenem pharmacokinetics in the abdominal cavity.

Funding

We did not receive any grant or fund for this study. We performed the study with our department budget (ordinary annual revenue) from Hiroshima University. This study was not sponsored by any company, including Shionogi & Co., Ltd (FINIBAX manufacturer).

Transparency declarations

None to declare.

References