Disposition, Metabolism, and Excretion of $^{14}$C]Doripenem after a Single 500-Milligram Intravenous Infusion in Healthy Men

Iolanda Cirillo,1* Geert Mannens,2 Cor Janssen,2 Marc Vermeir,2 Filip Cuyckens,2 Daksha Desai-Krieger,1 Nicole Vaccaro,1 L. Mark Kao,1 Damayanthi Devineni,1 Rebecca Redman,1 and Kenneth Turner1

Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, New Jersey,1 and Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen Pharmaceutica, N.V., Beerse, Belgium2

Received 31 March 2008/Returned for modification 18 May 2008/Accepted 16 July 2008

In this open-label, single-center study, eight healthy men each received a single 500-mg dose of $^{14}$C]doripenem, containing 50 μCi of $^{14}$C]doripenem, administered as a 1-h intravenous infusion. The concentrations of unchanged doripenem and its primary metabolite (doripenem-M-1) resulting from β-lactam ring opening were measured in plasma and urine by a validated liquid chromatography method coupled to a tandem mass spectrometry assay. Total radioactivity was measured in blood, plasma, urine, and feces by liquid scintillation counting. Further metabolite profiling was conducted on urine samples using liquid chromatography coupled to radiochemical detection and high-resolution mass spectrometry. Unchanged doripenem and doripenem-M-1 accounted for means of 80.7% and 12.7% of the area under the plasma total-radioactivity-versus-time curve (area under the concentration-time curve extrapolated to infinity) and exhibited elimination half-lives of 1.1 and 2.5 h, respectively. Total clearance of doripenem was 16 liters/h, and renal clearance was 12.5 liters/h. At 7 days after the single dose, 95.3% of total doripenem-related radioactivity was recovered in urine and 0.72% in feces. A total mean of 97.2% of the administered dose was excreted in the urine as unchanged doripenem (78.7% ± 5.7%) and doripenem-M-1 (18.5% ± 2.6%). Most of the urinary recovery occurred within 4 h of dosing. Three additional minor metabolites were identified in urine: the glycline and taurine conjugates of doripenem-M-1 and oxidized doripenem-M-1. These results show that doripenem is predominantly eliminated in urine as unchanged drug, with only a fraction metabolized to doripenem-M-1 and other minor metabolites.

Doripenem is a new parenteral carbapenem antibiotic with broad-spectrum activity against gram-negative and gram-positive pathogens, including strains resistant to multiple antibiotic classes (1, 6, 7). It is indicated for adults in the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis. Doripenem exhibits in vitro activity against contemporary strains of gram-negative bacteria that are often resistant, for serious, hospital-acquired infections, including Pseudomonas aeruginosa and extended-spectrum β-lactamase- and AmpC beta-lactamase-producing Enterobacteriaceae (10–12, 15, 19). In addition, doripenem is less likely than meropenem or imipenem to select for carbapenem-resistant strains of Pseudomonas aeruginosa (17). Because carbapenems produce time-dependent bactericidal activity, the ability to deliver doripenem via prolonged infusion increases the time that drug concentrations are likely to remain above the MIC for the infecting pathogen (2, 5). This may be of critical importance for difficult-to-treat pathogens that are not susceptible to other carbapenems or for which the MICs are near the susceptibility limits of the drug.

The present study was designed to characterize the disposition, metabolism, and excretion of doripenem in healthy men following a single 500-mg dose administered as a 1-h intravenous infusion, which is the standard doripenem dose indicated for treatment of subjects with serious bacterial infections. On the basis of clinical-trial data, the proposed dose of doripenem for treatment of moderate to severe infections is 500 mg administered by a 1-h or 4-h infusion (C. Lucasti, A. Jasiowich, O. Umeh, J. Jiang, and K. Kaniga, presented at the 17th European Congress of Clinical Microbiology and Infectious Diseases, 2007; O. Malafaia, O. Umeh, and J. Jang, presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2006; K. Naber, R. Redman, P. Kotey, L. Lorens, and K. Kaniga, presented at the 17th European Congress of Clinical Microbiology and Infectious Diseases, 2007).

MATERIALS AND METHODS

The study protocol was reviewed and approved by an independent ethics committee. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practices and all applicable regulatory requirements. All subjects participating in the study provided written informed consent.

Subjects. Eight healthy men characterized by a screening physical examination, medical history, vital signs, 12-lead electrocardiogram, laboratory testing, and normal renal function were enrolled. The study cohort had a median age of 20.5 years (range, 18 to 45 years), a median weight of 87.5 kg (range, 55 to 93 kg), and a median body mass index of 22.9 kg/m² (range, 19 to 28 kg/m²); all were Caucasian. Eligible patients had not smoked for at least 6 months and agreed to refrain from the use of medications, vitamins, and herbal supplements starting 2 weeks before $^{14}$C]doripenem administration. Patients also had to refrain from the use of tobacco and nicotine-containing products, alcohol, and foods containing poppy seeds starting 3 days before they reported to the study facility. Acer-
aminopenum was allowed up to 72 h before study drug administration, with a maximum dose of 500 mg three times a day or 3,000 mg per week. Additionally, subjects agreed to ingest only standardized meals and snacks provided by the clinical testing facility, to use a double-barrier method of birth control for 30 days after receiving the study treatment, and to refrain from donating blood for at least 60 days after the collection of the last blood sample. Subjects were excluded from the study if they presented with a history of allergy or hypersensitivity to β-lactam antibiotics, a history of drug or alcohol abuse, a relevant medical history, recent febrile illness or blood loss, a positive hepatitis B or C or human immunodeficiency virus test, recent treatment with an experimental drug or device, exposure to radiation within the last 12 months (other than dental or chest X-rays), or irregular defeation patterns.

**Study design.** This open-label, single-center, single-dose study consisted of a 12-day screening period, a 2-day baseline period, an 8-day treatment phase (infusion on day 1 and sample collections during day 8) with a possible extension for 7 additional days, and a posttreatment assessment. Subjects who met eligibility criteria during screening were admitted to the testing facility on the afternoon of day 2 to confirm their eligibility and undergo baseline measurements. Approximately 30 min after a standardized breakfast on day 1, subjects received a single 500-mg dose of doripenem via a 1-h intravenous infusion, which contained approximately 50 μCi (1.85 MBq) of [14C]doripenem (specific radioactivity, 3.7 kBq/mg). It was expected that intravenous administration of this dose of [14C]doripenem would result in a radiation exposure level below 500 μSv, constituting a minor level of risk. A standardized lunch, dinner, and light snack were served approximately 5, 9, and 12 h, respectively, after the start of the doripenem infusion. Subjects continued to receive standardized meals and snacks throughout the study and were required to drink at least 240 ml of water every hour up to 2 h after the study drug administration on day 1 and at least 1 h before the completion of each 24-h urine collection interval.

Blood, urine, and feces samples were collected after dosing on days 1 to 8. If the radioactivity in the 24-h urine collections on either day 6 or day 7 accounted for <2% of the total dose, or if fewer than 7 feces samples had been collected by day 8, then blood, urine, and feces samples were to be collected for an additional 7 days, and a subject was considered to have completed the study once the radioactivity in the two previous 7-day collection intervals accounted for <2% of the total administered dose and at least 7 postdose feces samples had been obtained. Subjects remained confined to the clinical testing facility until all required study assessments were completed on day 8 or, if necessary, during the extension period. Before discharge, subjects underwent a safety assessment, which included a physical examination, measurement of vital signs, clinical laboratory testing, and documentation of any concomitant medications. Subjects were contacted by telephone 1 week after discharge to evaluate the incidence, severity, and type of adverse events and to schedule a clinical evaluation if it was deemed necessary.

**Study drug.** The [14C]doripenem was radiolabeled on the 2-position of the azabicycloheptene ring of doripenem, which is metabolically stable in both the parent structure and the doripenem-M-1 metabolite. Ten individual intravenous infusion bags of 320 ml each of an aqueous formulation of [14C]doripenem (2 mg/ml; specific radioactivity, 3.7 kBq/mg) were prepared 1 day prior to dose administration. The intended specific activity of [14C]doripenem was obtained by dilution of [14C]doripenem with unlabeled doripenem. Doripenem powder and [14C]doripenem powder were each constituted with sterile water for injection and subsequently diluted in normal saline. A total volume of 250 ml, representing a doripenem dose of 500 mg and total radioactivity of 1.85 MBq (50 μCi), was administered to each subject.

**Pharmacokinetic assessments.** Blood samples were collected in heparinized tubes by direct venipuncture or via an indwelling catheter from a vein of the arm opposite to the one where doripenem was administered (to avoid any contamination by the study drug). Samples (8 ml) for pharmacokinetic and total 14C radioactivity determinations were collected before the start of doripenem infusion and at 15, 30, 45, 60, 75, 90, 105 min and 2, 3, 4, 6, 8, 12, 24, 36, and 48 h after that point. Additional 4-ml samples for measurement of total radioactivity in plasma were collected every 24 h thereafter. In addition, 16-ml blood samples for metabolite profiling and measurement of total radioactivity in blood were collected at 0, 1, 2, 4, 8, and 24 h.

Urine samples were collected over the following scheduled time intervals relative to the start of the study drug infusion: 0 to 4, 4 to 8, 8 to 12, 12 to 16, 16 to 24, 24 to 36, and 36 to 48 h, and then every 24 h until completion of the treatment phase. The total amount of urine collected during each time interval was thoroughly mixed before analysis. Feces samples were collected per stool in separate, preweighed, airtight plastic feces collection containers on all days during the time the subject remained at the clinical testing facility, or until seven postdose feces samples had been collected. All urine and feces samples were stored frozen until analysis.

**Safety assessments.** Safety was assessed from screening through the posttreatment telephone contact by evaluating the incidence, severity, and type of adverse events and their relationship to the study drug, as well as changes in clinical laboratory test results, physical examination findings, vital sign measurements, and concomitant need for medication or other therapy.

**Analytical procedures.** Concentrations of doripenem and the doripenem-M-1 metabolite in plasma were determined using validated liquid chromatography methods coupled to a tandem mass spectrometry (LC-MS-MS) assay. The doripenem and doripenem-M-1 peaks were detected with a turbo ion spray in the positive-ion mode on a triple-quadrupole mass spectrometer (API 5000). Chromatography was carried out on a Restek Allure PF2 propyl HPLC column (50 mm by 2.1 mm; particle size, 5 μm) under isocratic conditions with a mobile phase composed of water and acetonitrile containing 20 mM ammonium formate and 0.2% formic acid. In the doripenem-M-1 assay, chromatography was carried out on a Discovery HS F5 analytical HPLC column from Supelco (100 by 2.1 mm; particle size, 3 μm) under isocratic conditions with a mobile phase composed of acetonitrile and water containing 0.05% formic acid. Under these conditions, the retention time of doripenem was ~2.35 min and that of doripenem-M-1 was 3.60 min.

Concentrations of doripenem and doripenem-M-1 in plasma were determined simultaneously using a validated LC-MS-MS assay. Doripenem and doripenem-M-1 peaks were detected with a turbo ion spray in the positive-ion mode on a triple-quadrupole mass spectrometer (Applied Biosystems/MDS SCIEX; API 5000). Chromatography was carried out on a Restek Allure PF2 propyl HPLC column (50 mm by 2.1 mm; particle size, 5 μm) under gradient conditions, where mobile phase A was composed of acetonitrile and water containing 0.1% formic acid and 0.05% formic acid and mobile phase B was composed of acetonitrile containing 0.1% formic acid. Doripenem and doripenem-M-1 eluted at ~1.0 and 0.7 min, respectively.

The lower limits of quantitation (LLOQ) for doripenem and doripenem-M-1 in plasma were 0.10 μg/ml and 0.20 μg/ml, respectively, and the LLOQ for both in urine was 0.20 μg/ml.

Total 14C radioactivity was measured in blood, plasma, urine, and feces by liquid scintillation counting. Total radioactivity in plasma and urine was measured in duplicate samples following dilution with water and addition of Ultima Gold scintillation cocktail (Packard). Total radioactivity in blood was determined after combustion of quadruple dried 0.25-ml aliquots in a Packard sample oxidizer (model 307), with Permafluor used as the scintillation cocktail. Finally, total radioactivity in feces was determined in melatonin extracts as well as in combusted samples of the air-dried feces residues. Control samples of blood, plasma, urine, and feces were first spiked with a known amount of [14C]doripenem and then stored and processed with the actual samples in order to measure the recovery of total radioactivity. The LLOQ for [14C]doripenem were 0.53 to 0.54 μg/g in blood, 0.52 to 0.57 μg/g in plasma, and 0.10 to 0.11 μg/g in urine.

**Pharmacokinetic analysis.** Pharmacokinetic parameters for doripenem and doripenem-M-1 were estimated from the observed individual plasma and urine concentration-versus-time sampling by means of a noncompartmental analysis. Values for the following pharmacokinetic parameters were determined in plasma: Cmax (maximum observed concentration of the drug in plasma), Tmax (time to reach the maximum concentration of the drug in plasma); AUCinf (area under the concentration-time curve extrapolated to infinity); t1/2 (terminal elimination half-life, calculated as 0.693/λ), where λ is the elimination rate constant estimated by linear regression of the terminal points of the log-linear concentration-time profile), CL (total body clearance of doripenem, calculated as dose/(AUCt × V)), and V (apparent volume of distribution, calculated as dose/λ × AUCt). Pharmacokinetic parameters for which values were determined in urine included the total amount of drug excreted in urine (A), expressed both in milligrams and as a percentage of the administered dose, and renal clearance (CLr), calculated as the total cumulative amount of unchanged drug excreted into the urine (A) divided by the AUCt. Pharmacokinetic parameters calculated for total radioactivity included the Cmax, Tmax, AUCinf (area under the concentration-time curve from time zero to the last quantifiable concentration), AUCt, and t1/2 as well as the blood-to-plasma ratio of total radioactivity. In addition, the percentage of total radioactivity excreted in urine and feces was calculated as a percentage of the total [14C]doripenem dose.

**Metabolite profiling.** Metabolite profiling (structural identification and quantitative measurement) was conducted in urine using the LC-MS and LC-MS-MS methods described above. A single urine sample, collected from 4- to 8-h, and combined 8- to 24-h urine interval collection volumes were analyzed using radio-HPLC. Using a Waters Alliance HPLC 2695 system, the samples were chromatographed on an Atlantis C18 (5 μm; Waters) stainless steel column (25 cm by 4.6 mm [internal diameter]) with UV detection at 270 nm.
using a Waters 996 diode array detector. On-line radioactivity detection of the HPLC eluates was performed with a Berthold radioactivity monitor LB509 system. The eluates were mixed with Ultima Flo M scintillation cocktail, delivered by a Berthold LB 5035-3 pump at a flow rate of 4 ml/min. Column elution was started with a linear gradient at a flow rate of 1 ml/min with 100% solvent A (0.025 M ammonium acetate [pH 5.0]) to 90% solvent A with 10% solvent B (0.25 M ammonium acetate [pH 5.0])–methanol–acetonitrile [10/10/80, vol/vol/vol] over 25 min, followed by a linear gradient over 1 min to 100% solvent B. A QTOF Ultima mass spectrometer (Waters, Millford, MA) was used for metabolite identification. The mass spectrometer was equipped with a dual electrospray ionization probe and was operated in the positive-ion mode at a resolution of 8,000 (full width at half maximum at m/z 409). The source temperature was 100°C; the desolvation temperature was 250°C; and the cone voltage was set at 40 V. The second LockSpray electrospray ionization probe provided an independent source of the lock mass calibrant H₃PO₄⁻. The cluster ion at m/z 409.94184 was used as the lock mass in MS, whereas the ion at m/z 392.91534 (daughter ion of m/z 409.9) was used as the lock mass in MS-MS mode. Data were acquired in the centroid mode with a scan time of 1 s and were processed using Masslynx (version 4.1) software. The same chromatographic conditions were used as for the radio-HPLC analyses.

Combined peaks of doripenem-M-1 and two additional metabolites were collected after the initial HPLC run, evaporated, and then eluted by a second HPLC method. The evaporated samples were redissolved in water–acetonitrile (1:1, vol/vol) and then chromatographed on a ZIC-HILIC column (5 μm; Sequant) using the same radio-HPLC equipment as described above. Elution was started with a linear gradient at a flow rate of 1 ml/min from 5% solvent A (0.1% formic acid in water) and 95% solvent B (0.1% formic acid in acetonitrile) to 20% solvent A and 80% solvent B over 5 min, followed by continued elution in the latter solvent mixture for 30 min.

**RESULTS**

All eight subjects enrolled received the doripenem infusion and completed the study according to the protocol. The mean dose of doripenem administered was 500.7 mg (range, 490.5 to 512.0 mg), and the mean dose of radioactivity was 1.81 MBq (range, 1.74 to 1.88 MBq). Data from all eight subjects were included in the pharmacokinetic and safety analyses.

**Concentrations of doripenem and doripenem-M-1 in plasma and total radioactivity in plasma and blood.** Following intravenous infusion of doripenem, the total radioactivity in plasma paralleled the plasma doripenem concentration-versus-time profile (Fig. 1). The mean maximum total radioactivity in plasma of 22.9 μg/ml was generally achieved at the end of the 1-h infusion (Table 1), with a median Tₘₐₓ of 1.02 h. Comparison of the total radioactivity and plasma doripenem concentration-time profiles showed that unchanged doripenem accounted for most of the plasma radioactivity at the end of the infusion and then for 75% and 33% of the total radioactivity by 2 h and 6 h after administration, respectively. Total radioactivity levels in plasma and blood, as well as the plasma doripenem concentration, were below the LLOQ by 8 h.

Doripenem-M-1, the dicarboxylic acid metabolite resulting

**FIG. 1.** Mean (± standard deviation) concentrations of doripenem and doripenem-M-1 in plasma and total radioactivity in plasma and blood following a single 500-mg intravenous infusion of [¹⁴C]doripenem.

**TABLE 1.** Pharmacokinetic parameters of doripenem and doripenem-M-1 in plasma and of the [¹⁴C]-labeled moiety in plasma and whole blood following a single intravenous infusion of 500 mg [¹⁴C]doripenem.

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Mean value* (SD) for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doripenem in plasma</td>
</tr>
<tr>
<td></td>
<td>In plasma</td>
</tr>
<tr>
<td>Cₘₐₓ (μg/ml)</td>
<td>22.9 (2.37)</td>
</tr>
<tr>
<td>Tₘₐₓ (h) (median [range])</td>
<td>1.02 (1.00–1.02)</td>
</tr>
<tr>
<td>AUCₘₐₓ (μg · h/ml)</td>
<td>31.5 (4.51)</td>
</tr>
<tr>
<td>AUCᵢ (μg · h/ml)</td>
<td>31.8 (4.50)</td>
</tr>
<tr>
<td>t½ (h)</td>
<td>1.07 (0.125)</td>
</tr>
<tr>
<td>λz (h⁻¹)</td>
<td>0.0657 (0.0747)</td>
</tr>
<tr>
<td>CL (liters/h)</td>
<td>16.0 (2.23)</td>
</tr>
<tr>
<td>Vₘₐₓ (liters)</td>
<td>24.8 (5.80)</td>
</tr>
<tr>
<td>AUCᵢ ratio</td>
<td>0.0807 (0.0510)</td>
</tr>
</tbody>
</table>

*All parameters were assessed for a group of eight individuals. NAs, not assessable.

| For total radioactivity, the unit is microgram equivalents per milliliter.
| For total radioactivity, the unit is microgram equivalents times hour per milliliter.
| For doripenem, doripenem-M-1, and total radioactivity in plasma, t½ = time of last quantifiable concentration) ranged from 6 to 8 h; for total radioactivity in whole blood, t½ was equal to approximately 4 h for all subjects.
| Ratio of doripenem or doripenem-M-1 AUCᵢ to total radioactivity in plasma.
from β-lactam hydrolysis, was detected in plasma at much lower concentrations than those of unchanged doripenem (Fig. 2; Table 1). The $C_{\text{max}}$ of doripenem-M-1 averaged 1.56 μg/ml, which represented 6.8% of the $C_{\text{max}}$ of doripenem (22.9 μg/ml). The AUC$_{\text{oo}}$ of doripenem-M-1 averaged 4.98 μg·h/ml, which represented 15.7% of the AUC$_{\text{oo}}$ of doripenem (31.8 μg·h/ml). Overall, unchanged doripenem and doripenem-M-1 accounted for an average of 93.4% of the total radioactivity in plasma. Unchanged doripenem was the major drug-related component circulating in plasma, accounting for an average of 80.7% (range, 74.6 to 86.9%) of the total plasma radioactivity AUC$_{\text{oo}}$. The doripenem-M-1 metabolite accounted for an average of 12.7% (range, 11.3% to 14.0%) of the total plasma radioactivity AUC$_{\text{oo}}$.

The ratio of mean total radioactivity in blood to that in plasma ranged from 0.47 to 0.59 across the various time points, indicating that neither doripenem nor its metabolites were retained by cellular components in blood. Doripenem and doripenem-M-1 had mean $t_{1/2}$ values of 1.07 h and 2.54 h, respectively, and the $t_{1/2}$ of total radioactivity in plasma was between these values, at 1.59 h (Table 1).

**Total radioactivity in urine and feces.** By 7 days after dosing, 96.0% (range, 88.2% to 100.1%) of the administered dose of [14C]doripenem was recovered in urine and feces. Excretion of the radioactive dose was rapid and predominantly urinary, with a mean of 93.4% (range, 85.6% to 97.3%) of the radioactivity recovered in urine during the first 12 h after dosing, and 95.3% (range, 87.4% to 99.1%) of the radioactivity recovered by day 7. Excretion of the radioactive dose in feces amounted to only 0.72% (range, 0.45% to 1.02%) of the administered dose (Table 2).

Doripenem and doripenem-M-1 in urine. At 7 days after the infusion, the $A_{\text{ve}}$ for doripenem was 394.1 mg, representing 78.7% of the actual administered dose of doripenem, whereas the $A_{\text{ve}}$ for doripenem-M-1 was 92.9 mg, representing 18.5% of the administered dose. Therefore, a total of 487 mg, or 97.2% of the administered dose of doripenem, was excreted in urine as unchanged doripenem or doripenem-M-1. Urinary recovery of doripenem was complete within the first 24 h after dosing, with most of this recovery occurring within the first 4-h collection period. The CLR of doripenem and doripenem-M-1 averaged 12.5 and 18.9 liters/h, respectively.

**Metabolite profiling.** Although the major metabolite of doripenem was doripenem-M-1, three other peaks comprising less than 3% of the administered dose were quantified by radio-HPLC and identified by LC–MS-MS (Fig. 2). Two minor metabolites were identified as the glycine and taurine conjugates of doripenem-M-1, respectively. The last metabolite was identified by LC–MS-MS as oxidized doripenem-M-1, which was mainly present in urine samples collected 0 to 4 h after dosing.

Metabolite profiling was not conducted on fecal samples, due to the very low levels of radioactivity found upon initial analysis, or on plasma samples, inasmuch as doripenem and doripenem-M-1 accounted for the large majority of the radioactivity derived from [14C]doripenem, consistent with the findings in the urine samples.

**Safety.** Three of the eight subjects had treatment-emergent adverse events, all of which resolved before discharge from the clinical testing facility. One subject experienced diarrhea, and another experienced flatulence on day 1, which were considered by the investigator to be possibly related to the study drug. The other adverse event (dizziness on day 2) was considered to be unrelated to the study drug. None of the subjects had clinically significant changes in laboratory findings, vital signs, or physical examination findings.

**DISCUSSION**

The results of this study demonstrate that in healthy volunteers, doripenem is excreted almost exclusively in urine and predominantly as unchanged drug. Urinary recovery of total radioactivity accounted for 95.3% of the administered dose of doripenem, with only 0.72% of the dose found in feces. The

![Metabolic pathways of [14C]doripenem](image)

**FIG. 2.** Metabolic pathways of [14C]doripenem following intravenous infusion of a single 500-mg dose in healthy male subjects. Asterisks indicate the positions of the 14C label.

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Interval (h)</th>
<th>Mean (SD) % excretion of total radioactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>0–4</td>
<td>85.13 (4.28)</td>
</tr>
<tr>
<td></td>
<td>4–8</td>
<td>6.69 (1.01)</td>
</tr>
<tr>
<td></td>
<td>8–12</td>
<td>1.62 (0.22)</td>
</tr>
<tr>
<td></td>
<td>12–24</td>
<td>0.90 (0.12)</td>
</tr>
<tr>
<td></td>
<td>0–12</td>
<td>93.44 (3.98)</td>
</tr>
<tr>
<td></td>
<td>0–168</td>
<td>95.28 (4.03)</td>
</tr>
<tr>
<td>Feces</td>
<td>0–168</td>
<td>0.72 (0.21)</td>
</tr>
<tr>
<td>Urine + feces</td>
<td>0–168</td>
<td>96.00 (4.08)</td>
</tr>
</tbody>
</table>

**TABLE 2.** Percent excretion of total radioactivity in urine and feces of eight healthy male adult subjects after a single intravenous administration of 500 mg [14C]doripenem.
low recovery of radioactivity in feces indicates that biliary and/or intestinal excretion of doripenem in men is negligible. Unchanged doripenem accounted for most of the total radioactivity in plasma, averaging 80.7% on the basis of the AUC∞, and also accounted for most of the total radioactivity recovered in urine, averaging 78.7% of the administered dose of doripenem. In comparison, doripenem-M-1, the major metabolite of doripenem, accounted for an average of 12.7% of the plasma total radioactivity AUC∞ and 18.5% of the doripenem dose recovered in urine. Taken together, doripenem and doripenem-M-1 accounted for approximately 93% of the total radioactivity in plasma and 97% of the doripenem dose recovered in urine. These findings show that only a fraction of doripenem undergoes β-lactam ring hydrolysis to doripenem-M-1. Therefore, systemic exposure following doripenem infusion is mostly to unchanged doripenem.

Doripenem was metabolized to three additional biotransformation products besides doripenem-M-1, which collectively represented only a small fraction of the administered dose. The major metabolic pathway of doripenem was cleavage of the β-lactam ring to form the dicarboxylic acid metabolite doripenem-M-1 (Fig. 2). On the basis of LC-MS analysis, the three other metabolites represent further biotransformation products of doripenem-M-1 and include the glycine and taurine conjugates of doripenem-M-1 as well as an oxidation metabolite of doripenem-M-1, whose structure has not yet been conclusively elucidated. Because urinary recovery of doripenem and doripenem-M-1 accounted for 97% of the administered dose of doripenem, these three additional metabolites represent less than 3% of the administered dose.

The CL of doripenem and doripenem-M-1 averaged 12.5 liters/h (208 ml/min) and 18.9 liters/h (315 ml/min), respectively, which exceeded the glomerular filtration rate in these healthy volunteers. Thus, the renal elimination of doripenem and its major metabolite is controlled by glomerular filtration and not by renal tubular secretion.

Doripenem shares pharmacokinetic properties with other carbapenems, such as imipenem and meropenem (4). The level of binding of doripenem to human plasma protein is low (approximately 8%), like those of imipenem and meropenem (approximately <20%) (4). These carbapenems share generally dose-proportional pharmacokinetics over marketed dose ranges and a short elimination half-life of approximately 1 h. Ertapenem differs, with a high level of protein binding and consequently a nonlinear pharmacokinetic profile and a longer half-life than that of doripenem (Ivanz [ertapenem for injection] U.S. prescribing information; Merck & Co. Inc., February 2008). The disposition of doripenem, reported in this study, is comparable to that of other carbapenems, including imipenem/cilastatin, meropenem, and ertapenem (4, 8, 16, 18; U.S. prescribing information for Ivanz). The total radioactivity of doripenem in plasma paralleled the plasma carbapenem concentration shortly after infusion of a 14C-labeled carbapenem. Doripenem contains a methyl group at the C-1 position, which increases its stability toward hydrolysis by the renal enzyme dehydropeptidase-I (DHP-I) (14). Thus, most of the administered dose is excreted as unchanged drug. In contrast, imipenem is rapidly hydrolyzed by this enzyme and consequently must be administered in combination with cilastatin, an inhibitor of DHP-I, in order to achieve drug concentrations sufficient for antimicrobial activity (16).

The pharmacokinetics of doripenem in experimental animals, after administration at a dose of 20 mg/kg via an intravenous bolus injection, have been described recently (9). The AUC∞ was highest for dogs, followed by that for rabbits and monkeys, and was lowest for mice and rats, inversely paralleling the plasma clearance of the drug. The disposition of doripenem in humans reported in the present study most closely resembles that in dogs, in which the elimination half-life is 1 h, the plasma clearance is 4.7 ml/min/kg, the volume of distribution at steady state (Vd) is 0.26 liters/kg, and 83% of the administered dose is eliminated in the urine. Thus, as for other carbapenems, the disposition of doripenem is species dependent (13, 18).

In summary, doripenem is eliminated almost exclusively in urine and predominantly as unchanged drug. The major metabolite, doripenem-M-1, generated by cleavage of the β-lactam ring, accounts for a minor percentage of the administered dose circulating in plasma or recovered in urine. Three minor metabolites of doripenem-M-1 are detectable in urine, but at very low concentrations, and collectively they account for less than 3% of the administered dose. Therefore, the disposition of doripenem in human volunteers is largely comparable with that of currently available members of the carbapenem class, including imipenem/cilastatin and meropenem.

ACKNOWLEDGMENTS

We acknowledge MicroConstants, Inc., for the analysis of plasma drug concentration samples and Keystone Analytical Laboratories, Inc., for the analysis of urine drug concentrations. The CPU in Antwerp, H. Thierens (University of Gent, Gent, Belgium) is gratefully acknowledged for his contribution as a qualified radiopharmacist. We thank Milin Acharya for assistance in protocol development.

REFERENCES


