Serum, tissue and body fluid concentrations of tigecycline after a single 100 mg dose

Keith A. Rodvold, Mark H. Gotfried, Michael Cwik, Joan M. Korth-Bradley, Gary Dukart and Evelyn J. Ellis-Grosse

1Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, IL 60612, USA; 2College of Medicine, The University of Arizona, Phoenix, AZ 85012, USA; 3Pulmonary Associates, PA, 1112 E McDowell Road, Phoenix, AZ 85006, USA; 4IIT Research Institute, Life Sciences Group, 10 West 35th Street, Chicago, IL 60616, USA; 5Clinical Research, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA

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Objectives: The purpose of this study was to determine the tissue and corresponding serum concentration of tigecycline at selected time points in gall bladder, bile, colon, bone, synovial fluid (SF), lung and CSF in subjects undergoing surgical or medical procedures.

Methods: One hundred and four adult subjects (aged 24–83 years; 64 women, 40 men) received a single intravenous (iv) dose of tigecycline (100 mg infused over 30 min). Subjects were randomly assigned to one of four collection times at 4, 8, 12 and 24 h after the start of the infusion. For CSF, samples were collected at approximately 1.5 and 24 h after the start of the infusion. All subjects had serum samples collected before the administration of tigecycline, at the end of the infusion and at the time corresponding to tissue or body fluid collection. Drug concentrations in serum, tissues and body fluids were determined by LC/MS/MS. The area under the mean concentration–time curve from 0 to 24 h (AUC0–24) was determined for the comparison of systemic exposure between tissue or body fluid to serum.

Results: The mean serum concentrations of tigecycline were similar to those previously published. Tissue penetration, expressed as the ratio of AUC0–24 in tissue or body fluid to serum, was 537 for bile, 23 for gall bladder, 2.6 for colon, 2.0 for lung, 0.41 for bone, 0.31 for SF and 0.11 for CSF.

Conclusions: A single 100 mg dose of intravenous tigecycline produced considerably higher tissue/fluid concentrations in bile, gall bladder, colon and lung compared with simultaneous serum concentrations. On average, the systemic exposure of tigecycline in bone, SF and CSF ranged from 11% to 41% of serum concentrations. The results in bone are inconsistent with previous radiolabelled studies in animals and it is unclear if tight binding to bone (versus low bone uptake) or poor extraction of tigecycline for LC/MS/MS detection or both may have contributed to the differences we observed in humans.

Keywords: pharmacokinetics, pharmacodynamics, tissue penetration, glycylcyclines

Introduction

Tigecycline is a glycylcycline antimicrobial agent with an expanded broad-spectrum activity against Gram-positive and Gram-negative aerobes, anaerobic bacterial species and atypical pathogens.1 The in vitro activity includes susceptible and multidrug-resistant strains of Staphylococcus aureus, Streptococcus pneumoniae, vancomycin-resistant enterococci, extended-spectrum β-lactamase-producing Enterobacteriaceae and Bacteroides fragilis.1 In June 2005, the United States Food and Drug Administration approved tigecycline for the treatment of complicated intra-abdominal infections and complicated skin and skin-structure infections.2–4 The intravenous (iv) dosage of tigecycline for these infections is an initial dose of 100 mg, followed by 50 mg every 12 h.

The pharmacokinetic properties of tigecycline have been assessed in healthy adult subjects.2,5–7 The pooled mean (CV%) parameters after a single iv dose of tigecycline 100 mg include...
a maximum plasma concentration ($C_{\text{max}}$) of 1.45 mg/L (22%) and area under the plasma concentration-time curve (AUC) of 5.19 mg·h/L (36%). Tigecycline has a long elimination half-life of ~27 h (53%) and a total plasma clearance of 21.8 L/h (40%). Tigecycline exhibits a rapid distribution phase after iv administration, and a large apparent volume of distribution at steady-state of 568 L (43%). In vitro protein binding in human plasma has been reported to be concentration-dependent and ranges from 71% at 0.1 mg/L to 87% at 10 mg/L.

Clinical studies have evaluated the penetration of tigecycline into cantharidin-induced blister fluid, human polymorphonuclear neutrophils, epithelial lining fluid and pulmonary alveolar macrophages. The purpose of this study was to determine the tissue and corresponding serum concentration of tigecycline at selected time points in gall bladder (and bile if possible), colon, bone [and synovial fluid (SF) if possible], lung and CSF after a single iv dose of tigecycline 100 mg in subjects undergoing surgical or medical procedures.

Materials and methods

Study design and subjects

This was an open-label, single-dose study of tigecycline (Wyeth Pharmaceuticals Inc., Philadelphia, PA, USA) in subjects scheduled for gall bladder, colon, bone or lung surgery or a lumbar puncture procedure where appropriate tissue or body fluid samples were obtainable. Subjects undergoing an unscheduled lumbar puncture procedure were also considered for enrolment. The study was approved by the Institutional Review Board of participating study sites, and written informed consent was obtained from each subject before study entry. The study was conducted according to Good Clinical Practice guidelines.

Adult male and female subjects aged 18 years or older were considered eligible for this study. Female subjects could not be lactating or pregnant. If a woman was of child-bearing potential, the subject had to have a negative pregnancy test result and used a recommended method of birth control during and for a period of at least 1 month after tigecycline administration. Exclusion criteria included hypersensitivity to tigecycline or tetracyclines, any surgical or medical condition that may interfere with the distribution, metabolism or excretion of tigecycline, and participation in another investigational drug or medical device trial currently or within 30 days of study drug administration. Subjects were excluded in specific tissue collection groups if the following conditions were present: gall bladder: strong evidence preoperatively that the gall bladder was gangrenous; colon: ischaemic or inflammatory bowel disease, including ulcerative colitis and Crohn’s disease; bone: chronic osteomyelitis and lung: a pulmonary condition where a non-fibrotic or non-grossly emphysematous tissue sample could not be obtained.

Complete physical examination, including vital sign assessment, and medical histories from each enrolled subject were collected before receiving tigecycline. Physical examination was repeated at the end of the study, and information about adverse events was collected.

Subjects received a single iv dose of tigecycline 100 mg administered as a 30 min infusion before undergoing a surgical or medical procedure. The tigecycline infusion was started at approximately 1, 4, 8, 12 or 24 h before collection of tissue or fluid samples, according to the sample type assignment groups. All doses were administered via a controlled infusion pump, and exact infusion times were recorded.

Sampling times

The pre-specified sampling times for collection of gall bladder, colon, bone and lung tissue were at 4, 8, 12 or 24 h after the start of the tigecycline infusion. For the purposes of this study, tissue samples were taken from normal portions of resected tissue, and were considered healthy and non-inflamed samples. In subjects undergoing joint replacement surgery (n = 17), a SF sample was collected as soon as possible after surgical entry into the joint. A bile sample was also collected from all subjects undergoing gall bladder surgery. The collection times for CSF samples were at any time between the end of the tigecycline infusion and 24 h after the start of the tigecycline infusion. All subjects had blood samples collected for the determination of tigecycline serum concentrations at time zero (before the dose of tigecycline), at the end of the infusion (~30 min) and at the time corresponding to tissue or body fluid collection. The exact collection times for blood, tissues and body fluid samples were recorded and used in the data analyses.

Sample preparation procedures

Blood samples were centrifuged in a refrigerated centrifuge and serum was separated and stored at −70°C until the time of the assay. Tissue and body fluid samples were collected and stored immediately in an airtight container at −70°C until thawed and analysed. Tissue samples were thawed and blotted dry with clean absorbent paper. Accurately weighed tissue samples were prepared to determine tigecycline concentrations.

Tigecycline assay

Tigecycline concentrations in serum, tissues and body fluids were determined using a specific and sensitive liquid chromatography tandem mass spectrometry (LC/MS/MS) method. All drug assays were performed at the IIT Research Institute, Life Sciences Group, Chicago, IL, USA, and conducted according to Good Laboratory Practice guidelines. All samples, except bile fluid, were assayed within 13 months (range: 2–13 months) after the time of their collection. Bile samples were assayed within 18 months (range: 11–18 months).

Tigecycline was determined in human serum using an API 3000 LC/MS/MS system. A 0.20 mL aliquot of serum sample was mixed with 0.60 mL of internal standard solution ([t-butyl-d9] tigecycline, 150 ng/mL in acetonitrile). After vortexing and centrifugation, the supernatant was transferred to a clean culture tube and evaporated to dryness at room temperature under vacuum. The residue was reconstituted in 200 µL of mobile phase and a 10 µL aliquot was injected onto the LC/MS/MS system. Tigecycline and internal standard were eluted from a C18 HPLC column (Aquatasi C18, 50 × 2.1 mm, 5 µm, Keystone Scientific, Bellefonte, PA, USA) using a mobile phase consisting of water, acetonitrile, methanol and trifluoroacetic acid (78:16:6:0.1). Flow rate was 0.35 mL/min with a run time of 2 min. The standard curve was linear from 0.010 mg/L [lower limit of quantification (LLOQ)] to 2.0 mg/L. Quality control samples at concentrations of 0.025, 0.5 and 1.5 mg/L, prepared in human serum, were analysed during assay validation to assure acceptable precision and accuracy. Between-run precision and accuracy were 9% and 99% at 0.025 mg/L, 7% and 95% at 0.5 mg/L and 5% and 94% at 1.5 mg/L.

Tigecycline was determined in human SF and CSF using an LC/MS/MS assay similar to that used for serum. Phosphate-buffered saline (PBS) was used as a substitute matrix for both SF and CSF. A 0.20 mL aliquot of SF or CSF sample was mixed with 0.60 mL of internal standard solution ([t-butyl-d9] tigecycline, 150 ng/mL in...
Tigecycline tissue/fluid concentrations

Acetone. After vortexing and centrifugation, the supernatant was transferred to a clean culture tube and evaporated to dryness at room temperature under vacuum. The residue was reconstituted in 200 μL of mobile phase and a 10 μL aliquot was injected onto the LC/MS/MS system. The standard curve was linear from 0.01 mg/mL (LLOQ) to 20.0 mg/mL. Quality control samples were prepared at concentrations of 0.025, 0.5 and 1.5 mg/mL. Between-run precision and accuracy were 12% and 85% at 0.025 mg/mL, 5% and 95% at 0.5 mg/mL and 4% and 97% at 1.5 mg/mL.

Tigecycline concentrations were determined in human bone, lung, colon and gall bladder tissues using an LC/MS/MS assay similar to that used for serum. For calibrators and quality control samples, canine tissues were used as a substitute for human tissues, with canine colon being used as a substitute tissue for both human colon and gall bladder. A 0.20 g aliquot of tissue was mixed with 3 mL of internal standard solution ([l-butyld-9] tigecycline, 0.03 mg/mL in acetonitrile). Samples were homogenized using a tissue homogenizer (Tissue Tearor Model 398, Biospec Products, Inc, Bartlesville, OK, USA). After centrifugation, the supernatant was transferred to a clean culture tube and evaporated to dryness at room temperature under vacuum. The residue was reconstituted in 200 μL of mobile phase and a 10 μL aliquot was injected onto the LC/MS/MS system. The standard curves for each tissue were linear from 0.01 mg/kg (LLOQ) to 2.0 mg/kg. Quality control samples were prepared at 0.025, 0.5 and 1.5 mg/kg.

Between-run precision and accuracy for bone were 3% and 108% at 0.025 mg/kg, 2% and 99% at 0.5 mg/kg and 2% and 103% at 1.5 mg/kg. For lung, precision and accuracy were 6% and 109% at 0.025 mg/kg, 2% and 99% at 0.5 mg/kg and 2% and 106% at 1.5 mg/kg. For colon, precision and accuracy were 3% and 108% at 0.025 mg/kg, 3% and 98% at 0.5 mg/kg and 2% and 102% at 1.5 mg/kg.

Tigecycline was determined in human bile using an LC/MS/MS assay similar to that used for serum. For calibrators and quality control samples, canine bile was used as a substitute for human bile. A 0.02 mL aliquot of bile was mixed with 1.98 mL HPLC grade water. The diluted sample was mixed with 0.01 mL of internal standard solution ([l-butyld-9] tigecycline, 10 μg/mL in acetonitrile). A 0.02 mL aliquot of the diluted bile containing internal standard was then mixed with 0.03 mL of blank human serum that acted as a carrier for the tigecycline. The proteins in the bile–serum mixture were precipitated by the addition of 0.15 mL of acetonitrile. After vortexing and centrifugation, the supernatant was transferred to a culture tube and evaporated to dryness under a gentle stream of nitrogen at room temperature. The residue was reconstituted in 100 μL of mobile phase and a 10 μL aliquot was injected onto an LC/MS/MS system. The standard curves for each tissue were linear from 10 mg/L (LLOQ) to 800 mg/L. Quality control samples were prepared at 30, 100 and 500 mg/L. Between-run precision and accuracy were 5% and 97% at 30 mg/L, 5% and 102% at 100 mg/L and 5% and 97% at 500 mg/L.

Pharmacokinetic and statistical analysis

The area under the concentration–time curve from 0 to 24 h (AUC0–24) was determined for the comparison of systemic exposure between serum and tissue or body fluid. The AUC0–24 was determined with the linear/log trapezoidal method by using the microcomputer program WinNonlin Professional (version 4.1; Pharsight Corporation, Cary, NC, USA). For concentrations in serum, the means and medians from each available sampling time (e.g. 0.5, 4, 8, 12 and 24 h after start of the iv infusion for (CSF subjects: 0.5, 1 and 24 h]) were used to estimate an AUC0–24. The mean and median concentrations from site sampling times (e.g. 4, 8, 12 and 24 h for all sites (for CSF subjects: 1 and 24 h]) were used to estimate the AUC0–24 of the tissues or body fluids. A value of zero was used as the initial mean and median concentration at time zero for determination of the area term of serum, tissues and body fluids. The ratios between the site to serum were determined from concentration values of each subject and AUC0–24 values of each tissue or body fluid group.

Descriptive statistics (mean ± SD and median) are reported unless indicated otherwise.

Results

One hundred and fourteen adult subjects provided written informed consent. Six subjects were found to have an exclusion criterion and did not meet eligibility criteria. Among the remaining 108 subjects, four subjects were discontinued from the study because their surgery (two bone, two lung) was cancelled. A total of 104 subjects (64 female, 40 male) ranging in age from 24 to 83 years were included in the final pharmacokinetic analysis (Table 1).

Overall, tigecycline was well tolerated in the 108 subjects who received a single dose of tigecycline. No subject withdrew from the study because of any adverse event. Fifty-three (49%) subjects had at least one treatment-emergent related adverse event, including one that was severe. The most common mild to moderate drug-related adverse effects included nausea (n = 48) and vomiting (n = 14). In seven subjects, pruritus (6 mild to moderate, 1 severe) was described as a drug-related adverse effect. A 75-year-old man in the lung surgery group died from a cardiac arrest secondary to

Table 1. Demographic characteristics of 104 subjects receiving a single dose of 100 mg of tigecycline

<table>
<thead>
<tr>
<th>Tissue or body fluid group</th>
<th>No. of subjects of each sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Body mass index (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>64 f, 40 m</td>
<td>55 ± 17</td>
<td>169 ± 9</td>
<td>85.0 ± 18.6</td>
<td>29.9 ± 6.2</td>
</tr>
<tr>
<td>Gall bladder and bileb</td>
<td>22 f, 2 m</td>
<td>40 ± 11</td>
<td>163 ± 7</td>
<td>84.2 ± 15.7</td>
<td>31.6 ± 5.8</td>
</tr>
<tr>
<td>Colon</td>
<td>13 f, 11 m</td>
<td>60 ± 15</td>
<td>171 ± 8</td>
<td>82.8 ± 15.9</td>
<td>28.1 ± 4.7</td>
</tr>
<tr>
<td>Lung</td>
<td>5 f, 9 m</td>
<td>59 ± 16</td>
<td>175 ± 11</td>
<td>84.3 ± 20.7</td>
<td>28.2 ± 6.9</td>
</tr>
<tr>
<td>Boneb</td>
<td>12 f, 13 m</td>
<td>70 ± 8</td>
<td>169 ± 8</td>
<td>93.0 ± 22.1</td>
<td>32.3 ± 7.1</td>
</tr>
<tr>
<td>CSF</td>
<td>12 f, 5 m</td>
<td>43 ± 13</td>
<td>168 ± 12</td>
<td>77.9 ± 16.4</td>
<td>27.7 ± 5.4</td>
</tr>
</tbody>
</table>

f: females; m: males.

*Data are expressed as means ± SD (except for sex).

bThe same group of subjects provided the samples for gall bladder tissue and bile samples.

*The same group of subjects provided the samples for bone and synovial fluid samples.
gastrointestinal bleeding, 9 days after dosing with tigecycline. This was reported as a serious adverse event, however, not related to tigecycline use.

The serum concentration versus time profile of tigecycline after the start of infusion is illustrated in Figure 1. The serum tigecycline concentrations obtained before the study dose were below the quantitative limit (BQL) of detection in all subjects except one (15.8 ng/mL). The respective mean and median concentration values of tigecycline in serum immediately after the end of IV infusion were 1.94 and 1.32 mg/L (n = 103; range: 0.45–27.40 mg/L). Subsequent serum concentrations of tigecycline gradually declined to mean values of 0.22, 0.19, 0.11 and 0.07 mg/L at approximately 4, 8, 12 and 24 h, respectively.

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The mean (±SD) serum, site and ratios of site-to-serum concentrations at specific sampling times are listed in Table 2 and the AUC0–24 values for serum and various sites are listed in Table 3. The bile concentrations of tigecycline were obtained from 24 subjects undergoing a cholecystectomy, with 23 of 24 procedures being laparoscopic. All concentrations of tigecycline in bile (median: 75.2 mg/L; range: 15.9–1150 mg/L) were several log greater than concurrent serum concentrations (median: 0.112 mg/L; range: 0.042–0.250 mg/L) (Figure 2a). The ranges of mean and individual ratios of concentrations in bile to serum were 606–1997 and 123–7616, respectively. The respective site-to-serum ratios based on AUC0–24 for mean and median bile concentrations were 537 and 368.

### Table 2. Concentrations of tigecycline in serum, tissues and body fluids

<table>
<thead>
<tr>
<th>Site and sampling time (h)</th>
<th>No. of subjects</th>
<th>Serum (mg/L)</th>
<th>Site (mg/L or mg/kg)</th>
<th>Ratio (site:serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0.169 ± 0.041</td>
<td>308.6 ± 419.8</td>
<td>1997 ± 2808</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>0.153 ± 0.040</td>
<td>70.5 ± 45.0</td>
<td>606 ± 418</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>0.093 ± 0.024</td>
<td>148.1 ± 155.4</td>
<td>1753 ± 1795</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>0.066 ± 0.016</td>
<td>55.8 ± 50.5</td>
<td>822 ± 644</td>
</tr>
<tr>
<td>Gall bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0.169 ± 0.041</td>
<td>6.60 ± 6.59</td>
<td>38 ± 40</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>0.153 ± 0.040</td>
<td>6.26 ± 9.12</td>
<td>60 ± 104</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>0.093 ± 0.024</td>
<td>7.29 ± 7.88</td>
<td>85 ± 79</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>0.066 ± 0.016</td>
<td>7.52 ± 3.19</td>
<td>34 ± 37</td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0.297 ± 0.096</td>
<td>0.546 ± 0.345</td>
<td>2.3 ± 1.8</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>0.284 ± 0.245</td>
<td>0.470 ± 0.198</td>
<td>2.6 ± 1.4</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>0.139 ± 0.037</td>
<td>1.30 ± 2.43</td>
<td>11.9 ± 23.6</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>0.078 ± 0.029</td>
<td>0.575 ± 0.485</td>
<td>6.4 ± 4.6</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>5</td>
<td>0.197 ± 0.046</td>
<td>0.761 ± 0.669</td>
<td>3.7 ± 3.0</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>0.105 ± 0.026</td>
<td>0.232 ± 0.068</td>
<td>2.4 ± 1.0</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>0.083 ± 0.007</td>
<td>0.380 ± 0.260</td>
<td>4.5 ± 2.8</td>
</tr>
<tr>
<td>24</td>
<td>4</td>
<td>0.088 ± 0.103</td>
<td>0.401 ± 0.222</td>
<td>11.2 ± 4.0</td>
</tr>
<tr>
<td>Bone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0.198 ± 0.047</td>
<td>0.070 ± 0.043</td>
<td>0.35 ± 0.16</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>0.158 ± 0.035</td>
<td>0.078 ± 0.060</td>
<td>0.50 ± 0.35</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>0.098 ± 0.013</td>
<td>0.116 ± 0.132</td>
<td>1.10 ± 1.25</td>
</tr>
<tr>
<td>24</td>
<td>7</td>
<td>0.057 ± 0.016</td>
<td>0.090 ± 0.005</td>
<td>1.95 ± 0.17</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td></td>
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</tr>
<tr>
<td>4</td>
<td>5</td>
<td>0.196 ± 0.052</td>
<td>0.116 ± 0.059</td>
<td>0.58 ± 0.24</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>0.161 ± 0.051</td>
<td>0.071</td>
<td>0.34</td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>0.103 ± 0.012</td>
<td>0.091 ± 0.053</td>
<td>0.89 ± 0.49</td>
</tr>
<tr>
<td>24</td>
<td>5</td>
<td>0.061 ± 0.017</td>
<td>0.042 ± 0.011</td>
<td>0.71 ± 0.15</td>
</tr>
<tr>
<td>CSF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>11</td>
<td>0.306 ± 0.150</td>
<td>0.015 ± 0.003</td>
<td>0.055 ± 0.021</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>0.062 ± 0.018</td>
<td>0.025 ± 0.005</td>
<td>0.41 ± 0.07</td>
</tr>
</tbody>
</table>

aData are expressed as mean ± SD.

bData expressed as mg/L include bile, synovial fluid and CSF. Data expressed as mg/kg include gall bladder, colon, lung and bone.

cThree of six subjects had adequate samples available or concentrations equal to or above the quantitative limit of detection.

dFive of six subjects had concentrations equal to or above the quantitative limit of detection.

eFive of six subjects had adequate samples available for drug assay.

fThree of four subjects had adequate samples available for drug assay.

iOne of three subjects had adequate samples available for drug assay.

The mean (±SD) serum, site and ratios of site-to-serum concentrations at specific sampling times are listed in Table 2 and the AUC0–24 values for serum and various sites are listed in Table 3. The bile concentrations of tigecycline were obtained from 24 subjects undergoing a cholecystectomy, with 23 of 24 procedures being laparoscopic. All concentrations of tigecycline in bile (median: 75.2 mg/L; range: 15.9–1150 mg/L) were several log greater than concurrent serum concentrations (median: 0.112 mg/L; range: 0.042–0.250 mg/L) (Figure 2a). The ranges of mean and individual ratios of concentrations in bile to serum were 606–1997 and 123–7616, respectively. The respective site-to-serum ratios based on AUC0–24 for mean and median bile concentrations were 537 and 368.
The concentration–time profiles of tigecycline in colon tissue were similar: 6.60 and 0.04 to 0.25 mg/L (mean: 0.13 mg/L; median: 0.08 mg/L). Overall, the mean and individual ratios of concentrations in colon to serum varied from 0.58 to 0.89 and 0.23 to 1.61, respectively. The AUC_{0–24} site-to-serum ratios based on mean and median concentrations were 2.6 and 1.8, respectively.

Samples to measure tigecycline in serum and bone (Figure 2e) were obtained from 22 subjects requiring knee replacement surgery and three subjects undergoing shoulder or rotator cuff surgery. The majority of bone samples from the subjects requiring knee surgery were sawed from the femoral condyle and consisted of cancellous bone. Among the 25 bone samples, one was mislabelled and nine were reported to be BQL of assay detection. The majority of the BQL samples occurred during the later sampling times (e.g. three samples at 12 h and five samples at 24 h). The mean and median concentrations for the remaining 15 bone samples were 0.08 and 0.05 mg/kg (range: 0.03–0.27 mg/kg). In comparison, the mean and median concurrent serum concentrations were 0.14 and 0.13 mg/L (range: 0.04–0.25 mg/L). Overall, the mean and individual ratios of concentrations in bone to serum ranged from 0.04 to 0.25 mg/L, respectively. The site-to-serum ratio was 2.0 when AUC_{0–24} was calculated from either mean or median concentrations.

The individual concentrations in serum and SF in subjects undergoing knee replacement surgery are shown in Figure 2(f). The measured concentrations of tigecycline in SF ranged from 0.03 to 0.18 mg/L (mean: 0.08 mg/L; median: 0.065 mg/L). In comparison, the concurrent serum concentrations ranged from 0.04 to 0.25 mg/L (mean: 0.13 mg/L; median: 0.11 mg/L). The mean and individual ratios of concentrations in SF to serum ranged from 0.58 to 0.89 and 0.23 to 1.61, respectively. The respective site-to-serum ratios based on AUC_{0–24} for mean and median SF concentrations were 0.31 and 0.32.

Figure 2(g) displays the serum and CSF concentrations of tigecycline observed in the 17 subjects with non-inflamed meninges. The respective mean and median concentration of the 11 samples obtained between 0.92 and 2.1 h after the start of infusion was 0.015 and 0.014 mg/L (range: 0.011–0.020 mg/L). Individual ratios of CSF-to-serum concentration during the

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**Table 3.** Area under the concentration–time data and penetration ratio

<table>
<thead>
<tr>
<th>Tissue or body fluid group</th>
<th>Serum AUC_{0–24} (mg·h/L or mg·h/kg)</th>
<th>Site AUC_{0–24} (mg·h/L or mg·h/kg)</th>
<th>AUC_{0–24} ratio (site:serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile</td>
<td>2815/1787</td>
<td>5.24/4.26</td>
<td>537/368</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>119.99/65.96</td>
<td>5.24/4.26</td>
<td>23/14</td>
</tr>
<tr>
<td>Colon</td>
<td>17.30/9.83</td>
<td>6.58/5.46</td>
<td>2.6/1.8</td>
</tr>
<tr>
<td>Lung</td>
<td>9.19/8.02</td>
<td>4.58/3.99</td>
<td>2.0/2.0</td>
</tr>
<tr>
<td>Bone</td>
<td>2.05/1.26</td>
<td>4.95/4.49</td>
<td>0.40/0.28</td>
</tr>
<tr>
<td>Synovial fluid</td>
<td>1.68/1.58</td>
<td>5.35/4.86</td>
<td>0.31/0.32</td>
</tr>
<tr>
<td>CSF</td>
<td>0.460/0.426</td>
<td>4.18/3.59</td>
<td>0.11/0.12</td>
</tr>
</tbody>
</table>

AUC_{0–24} = area under the concentration–time curve from 0 to 24 h.

AUC_{0–24} or ratio determined from mean/median concentrations–time values.

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The AUC_{0–24} site-to-serum ratios based on mean and median concentrations–time values varied from 1.2 to 270. The site-to-serum ratios based on AUC_{0–24} for mean and median concentrations of gall bladder tissue were 23 and 14, respectively.

The concentration–time profiles of tigecycline in serum and colon tissue are illustrated in Figure 2(c). The colon concentrations of tigecycline were obtained from 24 subjects undergoing either a colectomy (n = 11), sigmoid and/or colon resection (n = 9) or colostomy (n = 4). The majority of tissue samples (n = 20) were obtained from either the descending or sigmoid portion of the large colon; the remaining samples were from either the ileum or caecum. Twenty-three of the 24 colon tissue samples were adequate for assay detection. The measured concentrations of tigecycline in colon tissue ranged from 0.07 to 6.23 mg/kg (mean: 0.73 mg/kg; median: 0.45 mg/kg). In comparison, the concurrent serum concentrations ranged from 0.04 to 0.78 mg/L (mean: 0.21 mg/L; median: 0.17 mg/L). Overall, the mean and individual ratios of concentrations in colon to serum varied from 2.3 to 11.9 and 0.1 to 59.9, respectively. The AUC_{0–24} site-to-serum ratios based on mean and median concentrations were 2.6 and 1.8, respectively.

The concentration–time profiles of tigecycline in serum and lung tissue are illustrated in Figure 2(d). The lung samples were obtained from 14 subjects undergoing either a lobectomy (n = 6), lobectomy and thoracotomy (n = 4), thoracotomy (n = 3) or pneumonectomy (n = 1). Thirteen of the 14 lung tissue samples were adequate for assay detection. The mean and median concentration values of tigecycline in lung and serum were 0.50 and 0.31 mg/kg (range: 0.11 – 1.89 mg/kg) and 0.13 and 0.11 mg/L (range: 0.02 – 0.25 mg/L), respectively. The mean ratios of lung to serum concentrations ranged from 2.4 to 11.2, whereas individual ratios varied from 0.5 to 14.6. The site-to-serum ratio was 2.0 when AUC_{0–24} was calculated from either mean or median concentrations.

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**Figure 1.** Serum concentration versus time profile following a single 100 mg dose of tigecycline. The y-axis is in the log scale. Filled grey circles represent serum concentrations obtained at the end of a 30 min infusion and open circles are serum concentrations obtained around the scheduled sampling times.
sampling period ranged from 0.016 to 0.095, with a mean of 0.055. In comparison, the respective mean and median concentration of the six samples obtained between 18.4 and 26 h after the start of infusion was 0.025 and 0.022 mg/L (range: 0.021–0.033 mg/L). Individual ratios of CSF-to-serum concentration during this sampling period ranged from 0.33 to 0.52, with a mean of 0.41. The site-to-serum ratios based on AUC_{0–24} for mean and median concentrations of CSF were 0.11 and 0.12, respectively.

**Discussion**

Our observed serum concentration–time data for a single 100 mg dose of tigecycline are in good agreement with previously published pharmacokinetic studies when differences in infusion periods (e.g. 30 versus 60 min) are accounted for.\(^5\)\(^–\)\(^7\) Serum concentrations of tigecycline demonstrated a steep decline after the end of infusion (Figure 1). Serum concentrations of tigecycline

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**Figure 2.** Individual concentrations of tigecycline in serum and bile (a), gall bladder (b), colon (c), lung (d), bone (e), synovial fluid (f) and CSF (g). The y-axis is in the log scale. Filled grey circles represent serum concentrations obtained at the end of a 30 min infusion, open circles are serum concentrations obtained around the scheduled sampling times, and filled black symbols are tissue or body fluid concentrations.
elimination in humans.5–7 The results of a previous mass balance study with biliary secretion being the major route of tigecycline excretion and 33% is excreted in urine as parent drug. 11 In that 59% of the radioactive dose is eliminated by biliary/faecal excretion and 33% is excreted in urine as parent drug.11 In addition, glucuronide conjugates accounted for ~5% and 4% of the radioactive dose detected in faeces and urine, respectively.

A limited amount of information is available regarding the pharmacokinetic–pharmacodynamic characteristics of tigecycline. A study conducted with a neutropenic murine-thigh infection model correlated the time above 0.5–4 times the MIC with a predictive parameter of efficacy.12 In addition, the AUC was correlated to clinical and microbiological outcomes in patients with complicated intra-abdominal infections.13,14

Tigecycline is currently being studied for the treatment of nosocomial and community-acquired pneumonia in hospitalized patients. Our results confirm that tigecycline penetrates into the lung after the administration of a single 100 mg dose. The concentrations of tigecycline in whole lung tissue were between 0.11 and 1.89 mg/kg. Only 1 of 12 subjects had a concentration of tigecycline in lung tissue that was less than that in serum. Because our study used whole lung tissue samples, intrapulmonary drug penetration into different compartments (e.g. extracellular and intracellular) of the lung could not be determined. However, a recent intrapulmonary penetration study has demonstrated that the concentrations of tigecycline in lung alveolar macrophages and epithelial lining fluid were 77-fold and 30% higher than that of serum, respectively.10 The higher intrapulmonary and lung concentrations of tigecycline should be beneficial for the treatment of lower respiratory tract infections attributable to susceptible pathogens.

To our surprise, the concentrations of tigecycline in bone were lower than anticipated (Table 2). In addition, concentrations of tigecycline in SF after a single dose were less than concurrent serum concentrations in 14 of 15 subjects. The majority of samples with bone concentrations above the quantitative limit of detection occurred during the first 12 h after drug administration. These results are inconsistent with previous animal studies for which [14C]tigecycline achieved high concentrations in bone.15 In rats given 3 mg/kg of [14C]tigecycline, the concentration of tigecycline in bone ranged from 4.1- to 45.6-fold higher than corresponding concentrations in plasma. It is unclear if tight binding to bone (versus low bone uptake) or poor extraction of tigecycline for LC/MS/MS detection or both, may have contributed to the differences we observed in humans. In addition, multiple doses may be needed to allow adequate accumulation of tigecycline into human bone (and SF).

This is the first study to report CSF penetration of tigecycline in humans. The CSF samples from our subjects without inflamed meninges were collected within hours after the end of the infusion and near the end of the 24 h study period. The individual CSF-to-serum ratios obtained between 18 and 24 h were higher (range: 0.33–0.52) than those determined a few hours after

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\begin{align*}
\text{Tigecycline tissue/fluid concentrations} \\
\begin{array}{cccccccccccc}
\text{Time (hours after start of the infusion)} & 0 & 2 & 4 & 6 & 8 & 10 & 12 & 14 & 16 & 18 & 20 & 22 & 24 & 26 & 28 \\
\text{Tigecycline concentration (mg/L)} & 0.01 & 0.1 & 1 & 10 & 100 & \\
\end{array}
\end{align*}
\]

Figure 2. continued.
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tigecycline administration (range: 0.016–0.095). The latter CSF-to-serum ratios are comparable with previous studies of tetracycline derivatives (e.g. oxytetracycline, demethylchlortetracycline, doxycycline), especially in subjects with non-inflamed meninges and where sampling occurred within 4 h after a single dose.16–18 However, CSF concentrations of doxycycline have reached 11–56% of serum concentrations after multiple doses were administered and in subjects with blood-brain barrier dysfunction.19–21 In addition, the magnitude of CSF concentrations for agents such as doxycycline (e.g. 0.10–2.00 mg/L) is significantly higher than that observed for tigecycline (e.g. 0.01–0.03 mg/L). Studies involving patients with inflamed meninges and after multiple doses should be performed before tigecycline is used for treatment of CSF infections.

We believe that our results are conservative and probably represent the minimal exposure of tigecycline concentrations in the various tissues and body fluids studied. Our subjects received a single dose of tigecycline whereas patients would normally receive multiple doses of tigecycline administered at a dosing interval of every 12 h. The observed accumulation of tigecycline in serum after multiple doses is approximately 3.4 for the 50 mg every 12 h regimen.19 It would be anticipated that site concentrations would also accumulate after multiple doses because a prolonged half-life of 20–40 h has also been observed in the serum as well as at extracellular and intracellular sites such as epithelial lining fluid and alveolar macrophages.6,19 In addition, tigecycline has exhibited a longer elimination half-life in tissues compared with plasma in animals.14 Changes in the physiological and pathological conditions of inflammation and/or infection in patients may also result in higher drug concentrations in serum and at the site of infection compared with subjects without these conditions. Obviously, further studies are warranted in patients with infections to confirm and explore the importance of tigecycline site concentrations, pharmacodynamic parameters and clinical outcomes.

In summary, the concentrations of tigecycline in the bile were several log greater than concurrent serum concentrations. This observation is not surprising as the biliary tract functions as the major route of drug excretion for this agent. After a single 100 mg dose of tigecycline, the average site-to-serum ratio (based on AUC0–24 values) was 23 for the gall bladder and 2 or greater for colon and whole lung tissues. In contrast to radioilabelled tigecycline studies in animals, the average site-to-serum ratios for bone and SF were only 0.41 and 0.31, respectively. Penetration of tigecycline into the CSF of subjects with uninfamed meninges was minimal, with CSF concentrations ranging from 0.011 to 0.033 mg/L and the average site-to-serum ratio based on AUC0–24 values was only 0.11. Further studies are needed to assess the impact of multiple doses on increasing the amount of tigecycline exposure in bone, SF and CSF.

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Transparency declarations

Drs J. M. K.-B., G. D. and E. J. E.-G. are employees of Wyeth Research.

References

Tigecycline tissue/fluid concentrations

