Tigecycline pharmacokinetic/pharmacodynamic update

Alasdair P. MacGowan*

Department of Medical Microbiology, Bristol Centre for Antimicrobial Research and Evaluation, University of Bristol and North Bristol NHS Trust, Southmead Hospital, Westbury-on-Trym, Bristol BS10 5NB, UK

This brief review summarizes recently published data on the pharmacokinetics and pharmacodynamics of tigecycline in man. Significant pharmacokinetic data are now available from the studies of infected patients, as is information on tissue distribution. Importantly, drug exposure–response relationships have been established for complicated skin and skin structure infections and intra-abdominal infection. These studies highlight the difficulties of undertaking pharmacodynamic studies in humans where account must be taken of both mixed pathogen infections and the potential impact of surgery. These data help to define the clinical role for tigecycline.

Keywords: human clinical trials, complicated skin and skin structure infection, complicated intra-abdominal infection

Introduction

The pharmacokinetics and pharmacodynamics of tigecycline have been reviewed on a number of occasions, usually as a single topic,1–3 but also in the context of the tetracycline class.4 Although these reviews have been published only recently, significant new information has become available on the pharmacokinetics of tigecycline in infected patients with complicated skin and skin structure infections (cSSSIs) and complicated intra-abdominal infection (cIAI). In addition, our understanding of the drug’s metabolism and excretion pathways has increased. Related to this are the data on pharmacokinetics in patients with renal and hepatic impairment. Also of great interest are the human pharmacodynamic data from clinical trials in cSSSI and cIAI, linking tigecycline drug exposure to clinical, microbiological and toxicological outcomes. These areas will form the basis of this review.

Pharmacokinetics

The pharmacokinetics of tigecycline have been extensively studied in patients recruited to Phase 3 studies of the therapy of cSSSI and cIAI. Using a non-compartmental approach, Darling et al.5 described 122 patients from three Phase 3 clinical studies comprising 107 with cIAI and 15 with cSSSI. Patients received a 100 mg loading dose of tigecycline followed by 50 mg every 12 h thereafter. Sampling occurred after at least six doses. The derived pharmacokinetic measures are shown in Table 1. As might be expected, there was more pharmacokinetic variation in these patients than in the small number of healthy volunteers studied in Phase 1 trials, as indicated by the larger percentage coefficient of variation (%CV). The lower $C_{\text{max}}$ (mg/L) values in patients with cSSSI compared with those with cIAI were related to the longer infusion (60 min) used in the cSSSI trial. Otherwise the kinetics were similar to those seen in healthy volunteers.

In a further study, Van Wart et al.6,7 developed a compartmental population pharmacokinetic model for tigecycline using pooled data from two Phase 2 studies in cSSSI and cIAI, involving 146 patients in total. Two dosing regimens were used in these Phase 2 studies, namely, a 100 mg loading dose followed by 50 mg every 12 h or a 50 mg loading dose followed by 25 mg every 12 h. Both two- and three-compartment models were evaluated using the non-linear mixed-effect model (NONMEM). The final model was used to generate $\text{AUC}_{0-12}$ values at steady state, which were used further in the pharmacodynamic evaluation of Phase 3 studies.8,9 A two-compartment model with zero-order input and first-order elimination best described tigecycline’s concentration–time data. Tigecycline clearance was greater in males and increased in proportion with creatinine clearances and weight. The AUC was shown to change in a corresponding manner, being lower in males and decreasing with increasing creatinine clearance and weight, as shown in Table 2. Despite the significance of the covariates, the changes in clearance were modest and are not thought to be a basis for changing dose regimens.

The metabolic and excretory routes of tigecycline have been further studied in man and animals using $^{14}\text{C}$tigecycline.1,10 In a human volunteer study, a single 100 mg dose was given followed by five 50 mg doses prior to a single $^{14}\text{C}$-labelled dose of tigecycline.10 Serum, urine and faecal samples were analysed by radio chromatography and a liquid chromatography (LC) assay in
tandem with mass spectrometry (MS). Metabolism and mass balance data were also obtained following single intravenous \(^{14}\text{C}\) tigecycline doses given to rats and dogs. In man, 59% of the radioactive dose given was excreted in the faeces and 32% in urine. Unchanged tigecycline was the predominant drug-related compound in each matrix, from all species. In human serum, conjugated metabolites of tigecycline and its epimer were detected as the major metabolites, accounting for 5% to 20% of serum radioactivity and 4% and 5% of dose excreted as conjugate in urine and faeces. Epimerization of tigecycline at C4 occurs via a non-enzymatic process producing a pharmacologically inactive compound. Although excretion occurs primarily in the form of the unchanged drug, two main metabolic pathways were identified, namely glucuronidation of parent to its epimer (metabolites M3 and M2) and amide hydrolysis of the compound. Although excretion occurs primarily in the form of the unchanged drug, two main metabolic pathways were identified, namely glucuronidation of parent to its epimer (metabolites M3 and M2) and amide hydrolysis of the \(^{14}\text{C}\) tigecycline doses given to rats and dogs. In man, 59% of the radioactive dose given was excreted in the faeces and 32% in urine. Unchanged tigecycline was the predominant drug-related compound in each matrix, from all species. In human serum, conjugated metabolites of tigecycline and its epimer were detected as the major metabolites, accounting for 5% to 20% of serum radioactivity and 4% and 5% of dose excreted as conjugate in urine and faeces. Epimerization of tigecycline at C4 occurs via a non-enzymatic process producing a pharmacologically inactive compound. Although excretion occurs primarily in the form of the unchanged drug, two main metabolic pathways were identified, namely glucuronidation of parent to its epimer (metabolites M3 and M2) and amide hydrolysis of the \(^{14}\text{C}\) tigecycline doses given to rats and dogs. In man, 59% of the radioactive dose given was excreted in the faeces and 32% in urine. Unchanged tigecycline was the predominant drug-related compound in each matrix, from all species. In human serum, conjugated metabolites of tigecycline and its epimer were detected as the major metabolites, accounting for 5% to 20% of serum radioactivity and 4% and 5% of dose excreted as conjugate in urine and faeces. Epimerization of tigecycline at C4 occurs via a non-enzymatic process producing a pharmacologically inactive compound. Although excretion occurs primarily in the form of the unchanged drug, two main metabolic pathways were identified, namely glucuronidation of parent to its epimer (metabolites M3 and M2) and amide hydrolysis of the \(^{14}\text{C}\) tigecycline doses given to rats and dogs. In man, 59% of the radioactive dose given was excreted in the faeces and 32% in urine. Unchanged tigecycline was the predominant drug-related compound in each matrix, from all species. In human serum, conjugated metabolites of tigecycline and its epimer were detected as the major metabolites, accounting for 5% to 20% of serum radioactivity and 4% and 5% of dose excreted as conjugate in urine and faeces. Epimerization of tigecycline at C4 occurs via a non-enzymatic process producing a pharmacologically inactive compound. Although excretion occurs primarily in the form of the unchanged drug, two main metabolic pathways were identified, namely glucuronidation of parent to its epimer (metabolites M3 and M2) and amide hydrolysis of the 

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**Table 1.** Non-compartmental pharmacokinetics of tigecycline in healthy volunteers and patients with cSSSI and cIAI

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>Healthy subjects (n = 5)</th>
<th>cIAI (n = 83)</th>
<th>cIAI (n = 24)</th>
<th>cSSSI (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>Healthy subjects mean (%CV)</td>
<td>cIAI mean (%CV)</td>
<td>cIAI mean (%CV)</td>
<td>cSSSI mean (%CV)</td>
</tr>
<tr>
<td>C\text{max} (mg/L)</td>
<td>0.621 (15)</td>
<td>0.794 (60)</td>
<td>0.837 (47)</td>
<td>0.40 (45)</td>
</tr>
<tr>
<td>C\text{min} (mg/L)</td>
<td>0.145 (16)</td>
<td>0.152 (47)</td>
<td>0.192 (47)</td>
<td>0.140 (52)</td>
</tr>
<tr>
<td>AUC\text{t} (mg h/L)</td>
<td>3.07 (12)</td>
<td>3.16 (46)</td>
<td>3.16 (46)</td>
<td>2.24 (40)</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>16.5 (12)</td>
<td>18.3 (37)</td>
<td>15.9 (36)</td>
<td>—</td>
</tr>
<tr>
<td>CL (L/h/kg)</td>
<td>0.204 (9)</td>
<td>—</td>
<td>—</td>
<td>0.313 (40)</td>
</tr>
<tr>
<td>(\text{AUC}_{\text{t}}) (mg h/L)</td>
<td>3.07 (12)</td>
<td>3.16 (46)</td>
<td>3.16 (46)</td>
<td>2.24 (40)</td>
</tr>
<tr>
<td>(\text{CL}_{\text{ss}}) (L/h/kg)</td>
<td>0.204 (9)</td>
<td>—</td>
<td>—</td>
<td>0.313 (40)</td>
</tr>
</tbody>
</table>

*\(a\) 30 min infusion.
*\(b\) 60 min infusion.
CV, coefficient of variation.

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**Table 2.** Population pharmacokinetic data for tigecycline based on a two-compartment model (50 mg dose)

<table>
<thead>
<tr>
<th>Patient characteristic and parameter</th>
<th>Number</th>
<th>(\text{AUC}_{\text{t}}) mean ± SD</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>77</td>
<td>2.60 ± 0.80</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>26</td>
<td>3.02 ± 0.70</td>
<td>+16.5</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal (&gt;80)</td>
<td>67</td>
<td>2.56 ± 0.67</td>
<td></td>
</tr>
<tr>
<td>mild (50–80)</td>
<td>28</td>
<td>2.73 ± 0.91</td>
<td>+6.7</td>
</tr>
<tr>
<td>moderate/severe (&lt;50)</td>
<td>8</td>
<td>3.78 ± 0.47</td>
<td>+47.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100</td>
<td>18</td>
<td>2.56 ± 0.11</td>
<td>−8.5</td>
</tr>
<tr>
<td>90–100</td>
<td>12</td>
<td>2.55 ± 0.79</td>
<td>−8.9</td>
</tr>
<tr>
<td>80–90</td>
<td>17</td>
<td>2.65 ± 0.82</td>
<td>−5.3</td>
</tr>
<tr>
<td>&lt;80</td>
<td>56</td>
<td>2.82 ± 0.59</td>
<td></td>
</tr>
</tbody>
</table>

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Pharmacodynamics

**Clinical and microbiological outcome studies in cSSSI**

Data from patients enrolled in three trials of cSSSI (one Phase 1 study and two Phase 3) were pooled for analysis. The doses used comprised a 100 mg loading dose, then 50 mg every 12 h iv, or a 50 mg loading dose followed by 25 mg every 12 h iv.
The previously described population pharmacokinetic model was used to calculate individual patient AUC_{ss} (mg.h/L). AUC_{ss}/MIC ratios were then evaluated as predictors of microbiological or clinical response. For the 50 mg loading dose regimen, the AUC_{ss} was 2.67 ± 0.99 mg.h/L (range 1.49–4.98) and the AUC/MIC ratio was 13.3 ± 13.5 (range 0.09–54.1). For the 100 mg loading dose regimen, the total drug AUC_{ss} was 5.46 ± 1.62 mg.h/L (range 2.81–9.36) and the AUC/MIC ratio was 33.4 ± 24.3 (range 0.21–102).

A wide range of pathogens was isolated from the clinical trial patients, including Gram-positive or Gram-negative aerobes as well as anaerobes. Some infections appeared to be monomicrobial while others were polymicrobial. Fifty-eight patients yielded 88 potential pathogens. To aid analysis, five patient cohorts were defined (Table 6).\(^8,17\) Cohorts 1 and 2 were too small for useful analysis. Pooled data from Cohorts 2 and 3 indicated that the AUC/MIC ratio was marginally predictive of microbiological outcome ($P = 0.1130$). The analysis was improved by the removal of an outlier patient (AUC 7.8 mg.h/L; AUC/MIC 65) with an *S. aureus* infection of a hernia repair where a prolene mesh had been surgically inserted and had not been removed. Addition of Cohorts 4, or 4 and 5, which included some pathogens for which tigecycline MICs were >1 mg/L (Cohort 4), had no significant effect on the AUC/MIC ratios; however, the magnitude of effect was decreased and so the final model included Cohort 2 plus 3.
Classification and regression tree (CART) analysis of this dataset indicated two possible AUC/MIC breakpoints, namely 12.5 or 16.4. Using an AUC/MIC ratio of 12.5, 32% (n = 7) of the patients with values below this level failed therapy, while 8% (n = 3) failed above. At an AUC/MIC ratio of 16.4, 30% (n = 8) of the patients failed below the ratio and 6% (n = 2) above. There was a 0.5 probability of cure at an AUC/MIC ratio of 10 and a 0.95 probability of cure at a ratio of 20–25 in terms of microbiological outcome. The two AUC/MIC ratios identified by the CART analysis were used in a Monte Carlo analysis to help determine a potential clinical breakpoint for \(S.\) \(aureus\). Given an AUC/MIC target of 12.5, the target attainment rates were: >99.99% if the MIC was ≤0.12 mg/L, 94.13% for MIC of 0.25 mg/L, 22.6% for MIC of 0.5 mg/L and ≤5% for MICs of ≥1 mg/L. At the higher AUC/MIC target of 16.4, the target attainment rate was: ≥99.9% for MICs of ≤0.12 mg/L, 74.5% for MIC of 0.25 mg/L and ≤5% for MICs of ≥0.5 mg/L. These data support a clinical breakpoint of 0.25–0.5 mg/L for \(S.\) \(aureus\).

Clinical and microbiological outcome studies in complicated intra-abdominal sepsis

An exposure–response analysis of the efficacy of tigecycline in patients with intra-abdominal sepsis was performed using pooled data from a single Phase 2 study and two Phase 3 trials. All patients were treated with a 100 mg loading dose, then 50 mg every 12 h iv. As with the pharmacodynamic studies of patients with cSSSI, a population pharmacokinetic model was used to calculate individual patient AUCss and, subsequently, AUC/MIC ratios. As the pathogens isolated were relatively heterogeneous, five cohorts of patients were defined depending on the pathogens isolated (Table 7). One hundred and twenty-three patients with 216 pathogens were included. The average patient age was 45 years +18 and the baseline APACHE II score was 6 +4.

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Cohorts 1 (n = 35), 2 (n = 24) and 3 (n = 47) were each too small for analysis and were therefore pooled for use in the CART analysis, which identified AUC/MIC breakpoints of 6.96 and 11.07. Using the AUC/MIC breakpoint of 6.96, there was a 94% chance of cure above this value and 60% below. There was a 90% chance of microbiological eradication with an AUC/MIC of 20–25. Clinical cure rates predicted by the model were 65% with an AUC/MIC ratio of 0 and 90% with a ratio of 20–25. This is presumably explained by the central role of surgery in the

### Table 7. Clinical cohorts of patients defined for the pharmacodynamic analysis of cIAI studies

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Pathogen</th>
<th>Number of patients (number of pathogens)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>monomicrobial (E.) (coli)</td>
<td>34 (35)</td>
</tr>
<tr>
<td>2</td>
<td>other monomicrobial or polymicrobial Gram-negative aerobic infection (\text{Klebsiella, Enterobacter and/or Citrobacter}) plus or minus (E.) (coli)</td>
<td>16 (24)</td>
</tr>
<tr>
<td>3</td>
<td>at least one Gram-negative pathogen and at least one anaerobic species</td>
<td>21 (47)</td>
</tr>
<tr>
<td>4</td>
<td>at least one Gram-negative pathogen and at least one Gram-positive species</td>
<td>21 (50)</td>
</tr>
<tr>
<td>5</td>
<td>all other mono or polymicrobial infection</td>
<td>31 (60)</td>
</tr>
<tr>
<td>1 + 2 + 3</td>
<td></td>
<td>71 (106)</td>
</tr>
</tbody>
</table>

Adapted from reference 9.
Tigecycline pharmacokinetics/pharmacodynamics

management of cIAI. When the AUC/MIC target of 6.96 was used in a Monte Carlo simulation, target attainment rates were: >93.89% for MIC of 0.5 mg/L, 27.2% for MIC of 1 mg/L and ≤5% for MICS of ≥2 mg/L. At the higher AUC/MIC target of 11.07, target attainment rates were: 100% for MICs ≤0.12 mg/L, 98.8% for MIC of 0.25 mg/L, 54.2% for MIC of 0.5 mg/L, 20.3% for MIC of 1 mg/L and ≤5% for MICS of ≥2 mg/L.19

Some caution is required in the use of these data to inform potential breakpoint setting in this particular indication where surgery is an important part of treatment, and the role of mixed infection is well recognized. These data, however, suggest a clinical breakpoint for Escherichia coli in the range 0.25–0.5 mg/L.

Adverse events

Using data from three single-dose pharmacokinetic studies in healthy volunteers, tigecycline AUC and Cmax were calculated in a non-compartmental analysis.20 Doses given to the volunteers were 12.5, 25, 50, 75, 100, 200 and 300 mg. Covariates in the analysis included age, weight, gender and geographical location. One hundred and thirty-six subjects were included; 38% reported nausea and 18% vomiting. In the final model, both increased AUC and Cmax predicted an increased incidence of nausea and vomiting. The median 50 mg dose AUC was 2.6 mg·h/L and corresponded to a probability of nausea of 0.26 and vomiting of 0.07. The median 50 mg dose Cmax was 0.39 mg/L and corresponded to a probability of nausea of 0.29 and vomiting of 0.11.

A similar analysis was performed on data from patients with cSSSIs enrolled in Phase 2 and 3 studies, who received a loading dose of 100 mg followed by 50 mg every 12 h or a 50 mg loading dose and 25 mg every 12 h.21 European location and 50 mg loading dose regimen was associated with lower risk of nausea and vomiting. However, neither the AUC nor Cmax could be related to nausea or vomiting. The reasons for this are unclear, but are probably related to the smaller dose range used in clinical trials than the earlier pharmacokinetic studies.

Conclusions

In conclusion, there are significant new data on the pharmacokinetics and pharmacodynamics of tigecycline in infected patients. Such data is central to refining the clinical role for tigecycline in the management of infection.

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References


Erratum

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In Table 4, the values in the last two columns are transposed. Hence, the tigecycline epimer values for urine, faeces and total should be $2.0 \pm 0.3$, $2.3 \pm 1.9$ and $4.3 \pm 3.8$, respectively, and the tigecycline values for urine, faeces and total should be $14.8 \pm 2.9$, $12.1 \pm 8.4$ and $26.9 \pm 9.3$, respectively. The author apologizes for this error.
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