Multiple-dose pharmacokinetics of intravenous telavancin in healthy male and female subjects

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Objectives: The aim of this study was to assess the steady-state pharmacokinetic parameters of telavancin, an investigational bactericidal lipoglycopeptide, after intravenous (iv) administration to healthy male and female subjects.

Patients and methods: In a randomized, double-blind, parallel-group, gender-stratified, two-dose study, 79 adult subjects received three daily 60 min iv infusions of telavancin at 7.5 mg/kg (n = 40) or 15 mg/kg (n = 39). Blood and urine samples were collected for pharmacokinetic analyses at admission, on day 3 pre-infusion and up to 48 h after the start of the day 3 infusion for 73 subjects (45 males and 28 females). Pharmacokinetic parameters were estimated by non-compartmental analysis.

Results: Following the day 3 telavancin dose (7.5 or 15 mg/kg), dose-proportional increases in mean peak plasma concentrations (Cmax, 88 versus 186 mg/L for low and high doses, respectively) and total systemic exposures (AUC0–24, 599 versus 1282 mg.h/L for low and high doses, respectively) were observed. Trough concentrations at steady state were 6 mg/L at 7.5 mg/kg/day and 16 mg/L at 15 mg/kg/day. The elimination half-life was dose-independent; the mean ± SD ranged from 6.0 ± 0.6 to 7.5 ± 1.3 h for low and high doses, respectively. Approximately two-thirds of the total telavancin dose was excreted unchanged in urine over 48 h. Pharmacokinetic parameters were similar in males and females.

Conclusions: Telavancin displayed linear plasma pharmacokinetics over the dose range 7.5–15 mg/kg/day and was primarily cleared via urinary excretion. No gender-related differences in the pharmacokinetic disposition of telavancin were observed. These data further characterize the pharmacokinetic profile of telavancin, a once-daily therapy targeted for the treatment of serious Gram-positive infections.

Keywords: antibiotics, Gram-positive bacteria, lipoglycopeptides, Phase 1

Introduction

Telavancin is an investigational bactericidal lipoglycopeptide with activity against clinically important Gram-positive pathogens, including methicillin-resistant Staphylococcus aureus (MRSA).1–4 In Phase 2 and 3 studies involving patients with complicated skin and skin structure infections caused by MRSA, intravenous (iv) administration of once-daily telavancin 10 mg/kg was at least as efficacious as vancomycin, with an acceptable safety profile.5–7 In an earlier Phase 1 study, telavancin pharmacokinetics were linear over the dose range 1–12.5 mg/kg, and steady state was achieved by 3–4 days, with no accumulation.8 A larger, randomized, placebo-controlled Phase 1 study in healthy volunteers (n = 160) was subsequently conducted in order to assess the safety and tolerability of telavancin, and, in particular, its effects on the QTc interval.9 This Thorough Electrocardiogram (ECG) Study revealed that 60 min infusions of telavancin 7.5 and 15 mg/kg/day for 3 consecutive days elicited a minimal placebo-adjusted, time-averaged 4–5 ms prolongation of the QTc interval relative to iv moxifloxacin 400 mg (~9 ms). Although there were no incidences of clinically significant ECG abnormalities at these telavancin dosages, the 15 mg/kg dose was associated with a greater incidence of adverse events (AEs; primarily taste disturbance, nausea, headache and vomiting). Here, we report additional results from this study, including a comparison of steady-state pharmacokinetics of multiple-dose telavancin 7.5 and 15 mg/kg in healthy male and female subjects.

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Telavancin pharmacokinetics in healthy subjects

Patients and methods

As described previously, this was a randomized, double-blind, two-dose, parallel-group, gender-stratified study approved by the Research Consultants’ Review Committee (Austin, TX, USA) and conducted in full compliance with the principles of Good Clinical Practice and the Declaration of Helsinki.

All subjects provided written, informed consent prior to enrollment. Eligible subjects were males and non-pregnant females aged 18–40 years, with body weight 50–100 kg and no clinically significant findings during clinical laboratory tests, physical examinations and ECGs at screening and admission. Subjects were admitted to the clinic 1 day prior to a 60 min, control iv infusion of 5% dextrose in water (D5W) for baseline ECG evaluations (day 0) and remained in the clinic until day 5. On days 1–3, subjects randomized to telavancin received daily 60 min infusions of telavancin 7.5 or 15 mg/kg. The clinic until day 5.

Demographic and baseline characteristics have been published previously. Of 79 subjects randomized to receive telavancin, 40 received telavancin 7.5 mg/kg and 39 received telavancin 15 mg/kg.

Day 3 pharmacokinetic data were available for 73 subjects (n = 39, telavancin 7.5 mg/kg; n = 34, telavancin 15 mg/kg); 6 subjects withdrew early after experiencing an AE during or immediately after the day 1 infusion.

Samples of blood (5 mL) were collected at admission, on day 3 pre-infusion and 30 min, 1, 2, 4, 6, 8, 12, 24, 36 and 48 h after the start of the infusion on day 3. Blood samples were stored on ice and then centrifuged (3000 rpm for 10 min, 2–8°C) to obtain plasma. Plasma samples were frozen at −60 to −80°C until assayed. Urine samples were collected at admission and on day 3 before infusion. Cumulative collections were then obtained following the day 3 infusion at 0–6, 6–12, 12–24, 24–36 and 36–48 h. Aliquots of urine samples were stored at −60 to −80°C until analysis.

All plasma and urine samples were analysed at Covance Bioanalytical Services LLC (Indianapolis, IN, USA) using a validated liquid chromatography–mass spectrometry method for telavancin; additionally, levels of THRX-651540 (the primary [7-OH] metabolite) were measured in urine. The method was linear for both telavancin and THRX-651540 over the range 0.25–100 mg/L, and the lower limit of quantification (LLQ) of telavancin and THRX-651540 was 0.25 mg/L.

Pharmacokinetic parameters of telavancin were determined by a non-compartmental analysis using WinNonlin Version 5.0.1 (Pharsight, Mountain View, CA, USA). For calculation purposes, concentrations of telavancin and the primary metabolite THRX-651540 below the LLQ were defined as 0 mg/L. Peak plasma concentration \( C_{\text{max}} \) and time to \( C_{\text{max}} \) (\( T_{\text{max}} \)) were the directly observed plasma pharmacokinetic parameters of telavancin at assumed steady state on day 3. The terminal elimination rate constant \( (\lambda_e) \) was estimated by linear regression of the natural logarithms of plasma concentrations versus time during the terminal phase. The terminal-phase elimination half-life \( (t_{1/2}) \) was calculated as \( \ln(2)/\lambda_e \). The area under the plasma concentration–time curve from 0 to 24 h \( (\text{AUC}_{0–24}) \) and the area under the first moment curve \( (\text{AUMC}_{0–24}) \) were calculated by the linear trapezoidal rule. Telavancin clearance at steady state \( (\text{CL}_{\text{ss}}) \) was calculated as \( \text{dose}/\text{AUC}_{0–24} \) on day 3. The mean residence time \( (\text{MRT}) \) was defined as the \( \text{AUMC}_{0–24}/\text{AUC}_{0–24} \). The apparent volume of distribution at steady state \( (V_{\text{ss}}) \) was calculated as the product of \( \text{CL}_{\text{ss}} \) and MRT. The total amount of telavancin and THRX-651540 excreted in urine (\( A_e \)) during the 24 h post-dose interval was calculated as:

\[
\sum_{i=0}^{t} U_i \times C_{U_i}
\]

where \( U_i \) and \( C_{U_i} \) are the urine volume and analyte concentration for time \( t \), respectively. Renal clearance \( (\text{CL}_R) \) was calculated as \( A_e/\text{AUC}_{0–24} \). Summary statistics (i.e. mean, SD, median, minimum, maximum and \( n \)) were performed for all pharmacokinetic parameters by treatment group.

Results

The demographics and baseline characteristics for the subjects included in the pharmacokinetic analysis from the two telavancin dose groups were similar to the data previously reported for all patients in these groups. No significant differences were found between the two groups of telavancin-treated subjects in the pharmacokinetic analysis. The mean ± SD age of subjects who received telavancin 7.5 and 15 mg/kg was 28 ± 5 and 27 ± 6 years, respectively. The mean ± SD subject weight was 70 ± 10 and 75 ± 12 kg, respectively. In total, 59% of the subjects in the 7.5 mg/kg group and 65% in the 15 mg/kg group were male.

Mean plasma telavancin concentrations peaked immediately at the end of the third 1 h infusion in both groups, before declining in an apparent bi-exponential manner. At each dose level, the mean telavancin concentration–time curves for men and women could almost be superimposed. Table 1 summarizes the steady-state pharmacokinetic parameters of telavancin 7.5 and 15 mg/kg/day stratified by sex. There were no differences between males and females in \( C_{\text{max}}, \text{AUC}_{0–24}, t_{1/2}, \text{CL}_{\text{ss}}, \text{MRT}, V_{\text{ss}} \) and \( \text{CL}_R \) at steady state. When the data for both sexes were combined, mean \( C_{\text{max}} \) (186 versus 88 mg/L) and trough plasma telavancin concentrations (16 versus 6 mg/L) were slightly more than 2-fold greater in the telavancin 15 mg/kg/day group than in the telavancin 7.5 mg/kg/day group. Total systemic exposure to telavancin at steady state also appeared to be proportional to the dose, with the mean \( \text{AUC}_{0–24} \) value in the high-dose group twice that of the low-dose group. Mean ± SD \( t_{1/2} \) was 6.0 ± 0.6 h in the telavancin 7.5 mg/kg/day group and 7.5 ± 1.3 h in the telavancin 15 mg/kg/day group (ranging from 4 to 10 h across all subjects). Mean \( \text{CL}_{\text{ss}} \) and \( \text{CL}_R \) values were similar in both groups. Renal clearance of telavancin was 65% to 72% of plasma clearance.

Expressed as a percentage of the daily dose, no statistically significant differences were detected in the mean 24 h urinary recovery of telavancin and THRX-651540 between male and female subjects (Table 2). Approximately two-thirds of the total telavancin dose was excreted as unchanged telavancin. The amount of THRX-651540 recovered from urine was ~6% of the dose at 7.5 mg/kg and ~3% of the dose at 15 mg/kg (Table 2).

Discussion

These data describe the pharmacokinetics of telavancin in subjects from a study of the effects of telavancin on cardiac repolarization. The plasma pharmacokinetic parameters of telavancin 7.5 and 15 mg/kg/day on day 3 were dose-proportional and consistent with those following a 7 day telavancin regimen at corresponding dosages. \( C_{\text{max}} \) and \( \text{AUC}_{0–24} \) values after administration of telavancin 15 mg/kg for 3 days were approximately double those after administration of telavancin 7.5 mg/kg. The analysis did not reveal any gender-related differences in telavancin plasma pharmacokinetics.
Table 1. Summary of telavancin pharmacokinetic parameters on day 3 (mean ± SD)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Telavancin 7.5 mg/kg</th>
<th>Telavancin 15 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n = 23)</td>
<td>Female (n = 16)</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>87.0 ± 14.5</td>
<td>88.2 ± 10.0</td>
</tr>
<tr>
<td>AUC_{0–24}</td>
<td>608 ± 104 (mg·h/L)</td>
<td>585 ± 86</td>
</tr>
<tr>
<td>$t_{1/2}$</td>
<td>6.1 ± 0.6</td>
<td>5.8 ± 0.6</td>
</tr>
<tr>
<td>CL$_{ss}$</td>
<td>13.0 ± 4.5</td>
<td>13.1 ± 1.8</td>
</tr>
<tr>
<td>MRT</td>
<td>8.9 ± 0.7</td>
<td>8.1 ± 0.8</td>
</tr>
<tr>
<td>$V_{ss}$</td>
<td>116 ± 40</td>
<td>106 ± 13</td>
</tr>
<tr>
<td>CL$_{R}$</td>
<td>7.9 ± 3.1</td>
<td>8.8 ± 4.9</td>
</tr>
</tbody>
</table>

$C_{\text{max}}$: maximum plasma concentration; AUC$_{0–24}$: area under the curve from time 0 to 24 h; $t_{1/2}$: terminal elimination half-life; CL$_{ss}$: clearance at steady state; MRT: mean residence time; $V_{ss}$: steady-state volume of distribution; CL$_{R}$: renal clearance.

Table 2. Urinary recoveries of telavancin and THRX-651540 (the primary metabolite) on day 3 (mean ± SD)

<table>
<thead>
<tr>
<th>Cumulative urinary recovery (0–24 h)</th>
<th>Telavancin 7.5 mg/kg</th>
<th>Telavancin 15 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n = 23)</td>
<td>Female (n = 16)</td>
</tr>
<tr>
<td>Telavancin (% dose)</td>
<td>62.9 ± 23.5</td>
<td>66.7 ± 33.2</td>
</tr>
<tr>
<td>THRX-651540 (% dose)</td>
<td>5.84 ± 1.30</td>
<td>6.14 ± 2.57</td>
</tr>
</tbody>
</table>

Telavancin had a mean $t_{1/2}$ ranging from 6.0 (7.5 mg/kg group) to 7.5 h (15 mg/kg group), with limited inter-individual variation in these healthy subjects with normal renal function. Plasma clearance at steady state was 12–13 mL/h/kg, with steady-state volume of distribution of 100–120 mL/kg (~7 L for a 70 kg subject). The results of this study also indicate that telavancin is predominantly excreted unchanged in the urine, with a limited contribution of the hydroxylated metabolite to the total urinary excretion. Renal clearance of telavancin was 8–10 mL/h/kg.

In conclusion, the steady-state pharmacokinetic profile of iv telavancin (7.5 and 15 mg/kg/day given as 1 h infusions) was further defined in this study and was shown to be similar in men and women. Systemic exposure was dose-proportional.

Acknowledgements

Part of this work was presented at the Forty-third Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, USA, 2003 (Poster A-20). A separate part of the study, which focused only on the effects of telavancin on the QTc interval, has also been published: Barriere S, Genter F, Spencer E et al. Effects of a new antibacterial, telavancin, on cardiac repolarization (QTc interval duration) in healthy subjects. J Clin Pharmacol 2004; 44: 689–95.

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Transparency declarations

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