Lack of Effect of Oritavancin on Warfarin Pharmacokinetics in Healthy Adult Subjects

S. Erlap Bellibas, Carlos Sanabria, Brooke Lohse, Karen Fusaro, Jeff Loutit, Michael N Dudley

The Medicines Company, Parsippany, NJ, USA; Spaulding Clinical, West Bend, WI, USA; The Medicines Company, San Diego, CA, USA

Abstract

Background: Oritavancin (ORI) is a novel lipoglycopeptide antibiotic and is currently in development as an alternative to β-lactam antibiotics for the treatment of vancomycin-resistant Gram-positive infections. A recent, open-label, single-center study by van der Linden et al. evaluated the pharmacokinetic (PK) interaction of ORI with warfarin, a substrate of CYP3A, CYP2C9, and CYP2C19. This post-hoc study aimed to further evaluate the PK interaction of ORI with warfarin using a modified design to elucidate whether exposure may be impacted and if an adjustment to warfarin dosing is warranted.

Methods: This was a randomized, open-label, single-center, single-blind, PK interaction study. Subjects were randomized to receive ORI 0.9 g intravenous infusion, when administered with warfarin, was generally well tolerated and no AEs of bleeding were reported.

Results: The PK parameters Cmax (3.000, 3.0000; 37.9) and AUC(0-inf) (3.000, 3.0000; 6.000) were not statistically different between Period 1 and Period 2 (Table 1). ORI did not affect the pharmacokinetics of warfarin as recommended in the FDA guidance “Drug Interaction Studies: Design, Data Analysis, Implications for Dosing, and Labeling Recommendations,” February 2012. No interaction was observed using the AUC(0-t) or the CYP2C9, CYP3A and CYP2C19 genotypes that were not available in this study.

Conclusions: ORI did not affect the PK of warfarin and warfarin did not affect the pharmacokinetics of ORI, thereby maintaining a single ORI dose in the presence of warfarin.

Introduction

The use of concomitant antibiotics and anticoagulants is common in patients with ABSSSI. However, the lack of understanding of the PK interaction of ABSSSI drugs and substrate drugs may not affect the pharmacokinetics of ORI, thereby maintaining a single ORI dose in the presence of warfarin.

Methods

Study Design

Subjects were randomized to one of three cohorts (Cohorts 1, 2, and 3) and received a single bolus injection of 0.9 g of ORI with or without warfarin at the start of the oritavancin infusion. The subjects had these samples collected again at 6, 12, 24, 36, 48, 72, 96, and 144 hours after the start of ORI infusion. The effect of ORI on warfarin exposure was evaluated within each cohort by comparing the PK parameters Cmax and AUC(0-inf) between Periods 1 and 2. ORI was administered concurrently with and up to 72 hours after warfarin.

Results

Table 1. Summary of S-Warfarin Plasma Pharmacokinetic Parameters by Cohort (PK Evaluable Population)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Geometric Ratio</th>
<th>LCL</th>
<th>UCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>Period 1</td>
<td>58157.8</td>
<td>3.000</td>
<td>3.000</td>
<td>3.000</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>Period 2</td>
<td>58157.8</td>
<td>3.000</td>
<td>3.000</td>
<td>3.000</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>Period 2</td>
<td>58157.8</td>
<td>3.000</td>
<td>3.000</td>
<td>3.000</td>
</tr>
</tbody>
</table>

Table 2. Summary of Effect of Oritavancin on the Pharmacokinetics of S-Warfarin: Point Estimates in Period 2 (S-warfarin + Oritavancin) Relative to Period 1 (S-warfarin Alone) and 90% Confidence Intervals

<table>
<thead>
<tr>
<th>Period</th>
<th>S-warfarin (PK Evaluable Population)</th>
<th>Point Estimates (90% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period 1</td>
<td>58157.8</td>
<td>3.000</td>
</tr>
<tr>
<td>Period 2</td>
<td>58157.8</td>
<td>3.000</td>
</tr>
</tbody>
</table>

Statistical Analysis of Drug-Drug Interactions

No statistically significant interaction was observed between Periods 1 and 2 (Figure 1). The PK parameters Cmax and AUC(0-inf) were not statistically different between Periods 1 and 2 (Table 2).

Summary and Conclusions

- Oritavancin did not affect the PK of S-warfarin when it was administered concurrently and up to 72 hours after the start of a single oritavancin infusion.
- Oritavancin and warfarin were well tolerated and no signs of bleeding were observed in this single dose design with both drugs in normal subjects.
- These data indicate that oritavancin does not affect the pharmacokinetics of warfarin: thus individualized warfarin dosing should be determined based on usual considerations, including monitoring for bleeding and monitoring of PT/INR in samples collected at least 12 hours following a single oritavancin dose.

Disclosures


References
