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Effect of Hepatic Impairment on the Pharmacokinetics of the Novel Glycopeptide Oritavancin

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ABSTRACT

Purpose. Oritavancin (ORI) is a semisynthetic glycopeptide being developed for the treatment of serious gram-positive infections. Physiochemical properties of ORI lead to extensive tissue distribution, with uptake by the tissues of the reticuloendothelial system, including the liver, lung, and spleen, while there is no evidence of metabolism. Due to ORI uptake by the liver, the effect of hepatic impairment on ORI pharmacokinetics was investigated in subjects with Child-Pugh Class B (moderate) liver insufficiency.

Methods. ORI was administered as a single dose of 800 mg over 90 minutes to 20 healthy subjects and 20 subjects with moderate hepatic impairment. Following the start of the infusion, plasma samples were collected at 45 and 85 minutes during the infusion, and at several timepoints post-infusion up to Day 45. Drug concentration was determined using an LC/MS/MS assay and noncompartmental PK analysis was performed for each group. ANOVA was used to compare the PK parameters ($AUC_{0-\infty}$, AUC_{0-24}, AUC_{0-t}, and C_{max}) between subject groups.

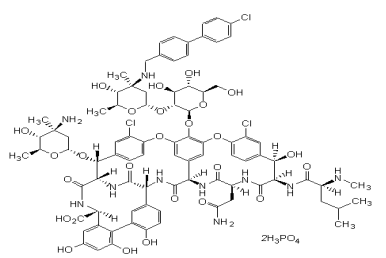
Results. AUC and C_{max} were lower in hepatically-impaired subjects compared with healthy subjects. Both $AUC_{0-\infty}$ and AUC_{0-t} were 14% lower, AUC_{0-24} was 11% lower, and C_{max} was 16% lower (Table 1). The 90% C.I. for ratios of $AUC_{0-\infty}$ (0.76–0.98), AUC_{0-t} (0.76–0.98), and AUC_{0-24} (0.77–1.02) were not within the pre-specified range of 0.80 to 1.25, thus equivalent exposure between subject groups could not be concluded. The 90% C.I. of the ratio for C_{max} (0.73–0.96) was within the range of 0.70 to 1.43, indicating that peak exposure was equivalent between treatment groups. Overall, ORI was well tolerated.

Conclusions. While the plasma AUCs were statistically significantly different for hepatically-impaired subjects versus healthy subjects, the observed relative differences are not clinically significant and would not warrant a dose adjustment for moderate hepatic impairment.

BACKGROUND

- Oritavancin
  - Novel glycopeptide antibiotic currently being developed for the treatment of complicated skin/skin structure infections
  - Bactericidal against clinically relevant gram-positive pathogens including those resistant to available antibiotics (*S. aureus* and *Enterococcus* spp., including methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci (VRE) strains)
- Pharmacokinetics
  - Highly lipophilic
  - Displays triexponential disposition
  - No evidence of metabolism
  - Linear pharmacokinetics with the dose range of 0.5 to 9.0 mg/kg (35 to 600 mg)
  - Approximately 86 to 90% bound to human plasma proteins
  - Extensive tissue distribution, with uptake by the tissues of the reticuloendothelial system (RES), including the liver, lung, and spleen
  - Approximately 5% and 1% of the dose is excreted in urine and feces, respectively, within two weeks following a single dose

Figure 1: Structure of Oritavancin



OBJECTIVE

- To explore the effect of hepatic impairment on oritavancin pharmacokinetics following a single IV 800-mg dose in subjects with Child-Pugh Class B (moderate) hepatic impairment compared with healthy subjects

METHODS

Study Design

Oritavancin was administered as an IV infusion
-- single 800-mg dose over 90 minutes

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Plasma sample collection times:
-- at 45 and 85 min. during infusion
-- at several times up to 24 hours post-dose, and
-- on Days 3, 4, 5, 8, 15, 21, 28, and 45

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Oritavancin plasma concentrations were determined using an LC/MS/MS assay

Pharmacokinetic Analysis

Noncompartmental PK Analysis
-- generated oritavancin PK parameters in each group:
C_{max}, T_{max}, k_{el}, $t_{1/2}$, AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$

↓

Statistical Analysis
-- 90% Confidence Intervals were constructed to compare ratios of log-transformed PK parameters:
C_{max}, AUC_{0-24}, AUC_{0-t}, and $AUC_{0-\infty}$
-- compare oritavancin exposure in plasma between subjects with moderate hepatic impairment and healthy subjects using the criteria of mean ratios within the ranges of 0.80 – 1.25 and 0.70 – 1.43 for AUC and C_{max}, respectively

RESULTS

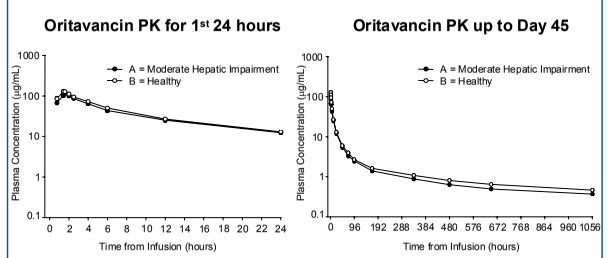
Table 1: Subject Demographics

	Hepatically Impaired Subjects (N=20)	Healthy Subjects (N=20)	Total (N=40)	P-value
Age (years)				
n	20	20	40	0.764[a]
Mean (SD)	52.5 (11.77)	51.3 (12.27)	51.9 (11.88)	
Gender				
Male	15 (75.0%)	15 (75.0%)	30 (75.0%)	1.000[b]
Female	5 (25.0%)	5 (25.0%)	10 (25.0%)	
Origin				
African Descent	2 (10.0%)	9 (45.0%)	11 (27.5%)	0.031[c]
Caucasian	17 (85.0%)	10 (50.0%)	27 (67.5%)	
Hispanic	1 (5.0%)	1 (5.0%)	2 (5.0%)	
Weight (kg)				
n	20	20	40	0.449[a]
Mean (SD)	83.15 (13.329)	80.27 (10.310)	81.71 (11.852)	
Height (cm)				
n	20	20	40	0.529[a]
Mean (SD)	169.17 (10.823)	171.38 (11.166)	170.27 (10.912)	
BMI (kg/m^2)				
n	20	20	40	0.184[a]
Mean (SD)	29.15 (4.783)	27.41 (3.226)	28.28 (4.123)	
Smoking Habit				
Smoker	12 (60.0%)	9 (45.0%)	21 (52.5%)	0.527[c]
Nonsmoker	8 (40.0%)	11 (55.0%)	19 (47.5%)	
Years Smoked				
n	12	9	21	0.020[a]
Mean (SD)	24.46 (14.260)	9.56 (11.791)	18.07 (14.985)	

[a] P-value obtained from one-way ANOVA for continuous variables
[b] P-value obtained from Fisher exact test
[c] P-value obtained from Pearson chi-square test with continuity correction

Figure 2: Oritavancin Pharmacokinetics in Subjects with Normal Hepatic Function and Moderate Hepatic Impairment

800 mg Dose



RESULTS (Continued)

Table 2: Noncompartmental Mean (%CV) PK Parameters for Oritavancin in Healthy Subjects and Subjects with Moderate Hepatic Impairment

PK Parameter	Hepatically Impaired Subjects (N=20)	Healthy Subjects (N=20)
$AUC_{0-\infty}$ (µg•h/mL)	2363 (31%)	2701 (22%)
AUC_{0-24} (µg•h/mL)	877 (37%)	947 (17%)
AUC_{0-t} (µg•h/mL)	1998 (31%)	2265 (19%)
C_{max} (µg/mL)	119 (22%)	145 (33%)
T_{max} (h)[a]	1.64 (1.42 – 2.50)	1.59 (0.75 – 1.73)
$t_{1/2}$ (h)	667 (26%)	617 (25%)
k_{el} (1/h)	0.0011 (22%)	0.0012 (20%)

[a] Median and range are reported.

Table 3: Statistical Comparison of the Rate (C_{max}) and Extent (AUC) of Exposure for Oritavancin in Healthy Subjects and Subjects with Moderate Hepatic Impairment

Parameter	Hepatically Impaired Subjects (N = 20)	Healthy Subjects (N = 20)	Ratio of Geometric Means	90% CI of Ratio
$AUC_{0-\infty}$ (µg•h/mL)	2276	2645	0.86	0.76 – 0.98
AUC_{0-24} (µg•h/mL)	829	933	0.89	0.77 – 1.02
AUC_{0-t} (µg•h/mL)	1922	2229	0.86	0.76 – 0.98
C_{max} (µg/mL)	117	139	0.84	0.73 – 0.96

Note: The comparison for each parameter was hepatically impaired versus healthy subjects.

- Subject characteristics were well balanced between the two treatment groups for age, body weight, BMI and smoking habit.
  - More men than women in both groups (75% vs. 25%)
  - Hepatically-impaired group: more Caucasians than African-Americans
  - Hepatically-impaired subjects smoked longer
- At every point measured, oritavancin plasma concentrations were approximately 10% to 15% lower in hepatically-impaired subjects.
- Total oritavancin exposure was approximately 14% ($AUC_{0-\infty}$ and AUC_{0-t}) and 11% (AUC_{0-24}) lower in hepatically-impaired subjects.
- Similarly, C_{max} was 16% lower in hepatically-impaired subjects.
- Equivalent exposure between subject groups could not be concluded.

RESULTS (Continued)

- The 90% C.I. for ratios of $AUC_{0-\infty}$ (0.76–0.98), AUC_{0-t} (0.76–0.98), and AUC_{0-24} (0.77–1.02) were not within the pre-specified range of 0.80 to 1.25.
- The 90% C.I. of the ratio for C_{max} (0.73–0.96) was within the range of 0.70 to 1.43, indicating that peak exposure was equivalent between treatment groups.
- Mean terminal plasma elimination half-life for hepatically-impaired subjects (~ 28 days) was slightly longer than that for healthy subjects (~26 days).

DISCUSSION AND CONCLUSIONS

- The rate and extent of oritavancin exposure was lower in hepatically-impaired subjects than in healthy subjects.
  - At every time point measured, mean oritavancin concentrations were lower in the hepatic impairment group, possibly due to differences in protein binding.
  - Since oritavancin is highly protein bound (~ 90%), a decrease in albumin concentrations due to hepatic impairment could trigger a transient increase in the free fraction of the drug.
  - The increased unbound oritavancin concentration would be available for redistribution to other body tissues.
  - Since oritavancin is widely distributed to tissues, mainly those of the RES, a transient elevation in free drug could be redistributed to the RES, which is not affected by hepatic impairment, resulting in a decrease in circulating drug, thus decreasing the amount of total drug measured.
  - Although lower protein leads to an increase in free drug and subsequently an increase in RES uptake, it does not appear to affect the apparent terminal plasma elimination half-life.
  - Although AUCs were marginally statistically significantly different from hepatically-impaired subjects compared with healthy subjects, the observed relative differences of 14% for $AUC_{0-\infty}$ and AUC_{0-t} and 11% for AUC_{0-24} are not clinically significant and would not require a change in dose for hepatically-impaired subjects.

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