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Interference of Oritavancin on Coagulation Tests as Assessed In Vitro and in a Phase 1 Study of Normal Healthy Volunteers

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Abstract

Background: Oritavancin (ORI) is a lipoglycopeptide (LG) antibiotic approved as a single-dose treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) caused by gram-positive pathogens. As some LG and lipopeptide (LP) antibiotics are known to interfere with phospholipid (PL)-dependent coagulation tests (CT), we assessed the effects of ORI on common CT and determined the time-to-resolution (TtR) of test interference.

Methods: For testing of clinical samples, plasma was obtained from normal healthy volunteers (NHV; n= 20) at defined time intervals following a 3h infusion of a single 1200 mg dose of ORI in a Phase 1 study. The TtR of each test interference was the interval from the start of the ORI infusion to the time the result returned to the normal reference range. For in vitro testing, ORI was spiked into human plasma over a concentration range of 2 to 47 µg/ml. PL-dependent CT included prothrombin time (PT), activated partial thromboplastin time (aPTT), Dilute Russell Viper Venom Test (DRVVT), activated clotting time (ACT), silica clot time (SCT) and activated Protein C Resistance (APCR). PL-independent CT included chromogenic anti-factor Xa (anti-FXa), thrombin time (TT) and an assay to diagnose heparin-induced thrombocytopenia (anti-heparin-PF4).

Results: Transient prolongation of PT, aPTT, DRVVT, ACT and SCT occurred in plasma samples obtained from NHVs in the phase 1 study (table). Using ORI-spiked human plasma in vitro, prolongation of coagulation in the affected tests occurred in a concentration-dependent manner. ORI did not interfere with assays for APCR, anti-FXa, TT, or anti-heparin-PF4.

Conclusion: Although ORI has no effect of the coagulation system, it can cause artificial elevations in some laboratory CT. Because of its single-dose regimen, the transient interference of ORI on these CT does not require further consideration beyond the specified TtR of test interference in contrast to some LG and LP antibiotics that require daily administration.

Coagulation test	Time-to-resolution (hours) of test interference in normal healthy volunteers that received a single 1200 mg infusion of oritavancin
Phospholipid-dependent	
PT	12
APTT	120
ACT	24
SCT	18
DRVVT	72
APCR	unaffected
Phospholipid-independent	
Anti-FXa	unaffected
TT	unaffected
Anti-Heparin-PF4	unaffected

Background

Oritavancin is a lipoglycopeptide antibiotic approved as a single-dose treatment of adult patients with acute bacterial skin and skin structure infections caused by gram-positive microorganisms (1-3). Oritavancin has been proven to be efficacious as a single-dose regimen due to its unique pharmacokinetic and pharmacodynamic properties, including a long terminal half-life in plasma of 245 h and potent concentration-dependent bactericidal activity (1).

Previous studies have shown that some lipoglycopeptide or lipopeptide antibiotics (e.g., telavancin, daptomycin), may artificially prolong phospholipid-dependent coagulation tests (4-7). Although these agents do not interfere with the coagulation system in vivo, their interference with coagulation assays can confound monitoring of hemostasis in the clinical setting. The potential for oritavancin to cause interference with phospholipid-based tests may therefore occur for a period following administration of a single once-only dose. Thus, the effect of oritavancin on commonly used phospholipid-dependent and -independent coagulation assays was determined using in vitro methodologies. This was followed by a phase 1 clinical study to determine the maximum time-to-resolution of test interference in plasma obtained from normal healthy volunteers who received a single 1200 mg dose of oritavancin.

Methods

Coagulation Testing In Vitro

Oritavancin powder (The Medicines Company, Parsippany, NJ) was dissolved into NERL™ Reagent Grade Water (ThermoFisher Scientific, Waltham, MA) and then diluted in pooled normal plasma (George King BioMedical Inc., Overland Park, KS) to achieve targeted nominal concentrations of 0 (control), 2, 5, 8, 15, and 45 µg/mL (the in vitro solubility limit in human citrated plasma). Oritavancin concentrations in each sample of citrated human plasma were determined using a qualified liquid chromatography method with tandem mass spectrometric (LC-MS/MS) detection (calibration range, 0.5-300 µg/mL; method on file, The Medicines Company ; assayed oritavancin concentrations of 2.1, 5.4, 8.3, 15.9, and 46.6 µg/mL were obtained and appear in Table 1). Each sample was tested in triplicate on three separate days in the indicated coagulation tests following the manufacturers' protocols.

Phase 1 Clinical Study

The phase 1, open-label, single-center, single-arm clinical study was conducted to examine the effects of a single 1200 mg intravenous dose of oritavancin on multiple phospholipid-dependent and phospholipid-independent coagulation tests in normal healthy volunteers 18 to 65 years of age. Subjects were required to have a body mass index <45 kg/m^2 and were excluded if PT/INR, aPTT, or ACT coagulation test results were outside of the normal reference range at baseline (pre-dose). Subjects received a single oritavancin infusion of 1200 mg over 3 h.

Plasma samples were collected at 0, 3, 6, 12, 18, 24, 48, 72, 96, and 120 h after the start of oritavancin infusion and were stored at -20ºC until analyzed. Oritavancin concentrations in each sample of citrated human plasma were determined using the qualified liquid chromatography method indicated above. The oritavancin concentration-time profile determined in the phase 1 study was compared to that obtained in patients undergoing treatment with a single 1200 mg dose of oritavancin for ABSSSI infections (see Figure 1) in the SOLO phase 3 studies (8).

Phospholipid-dependent coagulation tests included the indicated reagents for PT/INR and aPTT along with DRVVT (Instrumentation Laboratory, Bedford, MA), ACT (Accriva Diagnostics, San Diego, CA), and SCT (HemosIL® Silica Clotting Time, Instrumentation Laboratory). Phospholipid-independent coagulation tests included anti-FXa (STA®-Rotachrom® Heparin) and D-dimer (HemosIL® D-dimer HS 500, Instrumentation Laboratory). Coagulation tests were performed following the protocols provided by the manufacturers.

The primary objective of the study was to determine the time-to-resolution of test interference (mean, median, minimum and maximum values), defined as the interval from the start of the oritavancin infusion to the time the result for all subjects returned to the normal reference range or below the subject's baseline value for each coagulation test. The secondary objective was to determine the relationship between oritavancin plasma levels and effects on coagulation tests.

Coagulation parameters were summarized using the pharmacodynamic-evaluable (PE) population, defined as all subjects who received study drug, had a baseline coagulation test value, and had a post-baseline coagulation test value that was adequate to determine the time-to-resolution of elevations. For the secondary endpoint (relationship between oritavancin plasma levels and effects on coagulation tests), a logistic regression model was constructed to assess the risk of a clinically significant alteration in a coagulation parameter (ie, values outside the normal reference range) using drug concentration as a continuous independent variable.

Results

Table 1. Interference by oritavancin in phospholipid-dependent coagulation tests in vitro occurs in a concentration-dependent manner.

Coagulation test	Reagent	Test Units	Test Reference Range	Mean ± SD and Percent Change Relative to Control (%) at the Indicated Oritavancin Concentration[a]					
				Control	2.1 µg/mL	5.4 µg/mL	8.3 µg/mL	15.9 µg/mL	46.6 µg/mL
Phospholipid-dependent									
PT/INR	STA®-Neoplastine CI Plus	Seconds	11.9-14.1	13.2±0.17	13.2±0.16 (0)	13.2±0.13 (0)	13.2±0.11 (0)	13.4±0.13 (1.4)	13.7±0.11 (3.6)
PT/INR	HemosIL® RecombiPlasTin 2G	Seconds	9.4-12.5	12.1±0.11	12.1±0.14 (0.2)	12.2±0.10 (1.1)	12.3±0.15 (1.9)	12.4±0.16 (2.3)	13.2±0.18 (8.9)
PT/INR	Dade® Innovin®	Seconds	9.9-11.8	11.0±0.06	11.0±0.06 (0)	11.1±0.07 (0.6)	11.1±0.05 (1.0)	11.3±0.12 (2.5)	11.8±0.07 (7.0)
aPTT	STA®-PTTa	Seconds	23.4-36.4	31.8±0.40	31.7±0.35 (–0.2)	32.5±0.72 (2.2)	33.3±0.63 (5.0)	36.3±0.54 (14.4)	59.8±2.28 (88.3)
aPTT	HemosIL® SynthASil	Seconds	25.1-36.5	31.7±0.28	32.0±0.16 (0.9)	32.2±0.19 (1.5)	32.7±0.20 (3.3)	34.1±0.19 (7.6)	42.5±0.58 (34.2)
aPTT	Dade® Actin® FSL	Seconds	25.3-33.8	29.5±0.61	29.5 ± 0.25 (–0.2)	29.6±0.28 (0.2)	29.7±0.30 (0.7)	30.4±0.50 (2.8)	39.8±0.85 (34.8)
DRVVT	LA Check™/LA Sure™	Seconds	<55.1	43.2±1.07	43.6±0.98 (0.9)	43.4±1.06 (0.5)	44.3±0.90 (2.6)	44.8±0.93 (3.7)	53.6±1.72 (24.0)
APCR	COATEST™ APC™ Resistance V	APC ratio	2.2-4.0	2.3±0.11	2.3±0.11 (0)	2.3±0.10 (1.3)	2.3±0.11 (1.7)	2.3±0.09 (2.2)	2.4±0.13 (3.1)
Phospholipid-independent									
Anti-Factor Xa	STA®-Rotachrom Heparin	IU/mL	LLOQ<0.10 IU/mL	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ
Thrombin time	STA®-Thrombin	Seconds	<20.0	15.6±0.21	15.6±0.18 (0.3)	15.8±0.27 (1.2)	15.7±0.15 (1.0)	15.7±0.24 (0.9)	15.7±0.33 (0.9)
Anti-Heparin-PF4	Asserachrom® HPIA	Norm. OD ratio	<0.8	Negative[b]	Negative	Negative	Negative	Negative	Negative
D-dimer	STA®-Liatest® D-Di	µg/mL FEU	<0.5 µg/mL FEU	0.21±0.04	0.25±0.04 (19.0)	0.22±0.05 (4.8)	0.25±0.05 (19.0)	0.25±0.04 (19.0)	0.29±0.04 (38.1)

Abbreviations: PT/INR, Prothrombin Time/International Normalized Ratio; aPTT, Activated Partial Thromboplastin Time; DRVVT, Dilute Russell's Viper Venom Test; APCR, Activated Protein C Resistance; IU, International Units; Norm. OD ratio, Normalized Optical Density Ratio; FEU, Fibrinogen Equivalent Units; LLOQ, Lower Limit of Quantitation. [a]Coagulation test values in **red text** exceed the indicated assay normal reference range. [b]A normalized OD ratio of <0.8 is indicative of negative for heparin-induced platelet antibodies.

Figure 1. The oritavancin concentration-time profiles determined in subjects (n=20) in the phase 1 study and from patients in the SOLO phase 3 studies are comparable.

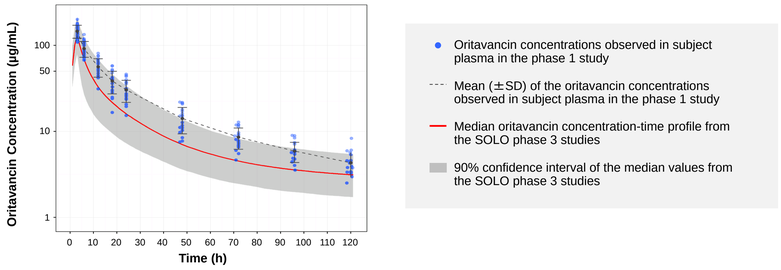

Figure 2. Increases in PT or aPTT in the phase 1 study are dependent on the oritavancin plasma concentrations determined in subjects.

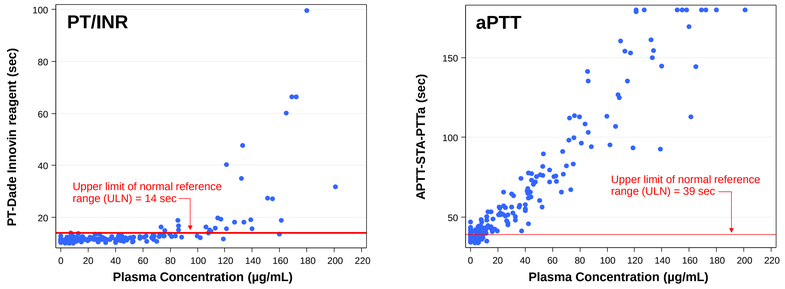

Table 2. Oritavancin causes variable prolongation of the phospholipid-dependent assays PT/INR or aPTT determined in plasma from subjects in the phase 1 study.

Coagulation test	Reagent	Time-to-resolution[a] (h)	
		Mean (SD)	Median (Min, Max)
PT/INR	STA®-Neoplastine CI Plus	0.0 (0.0)	0.0 (0.0, 0.0)
	HemosIL® RecombiPlasTin 2G	1.5 (2.7)	0.0 (0.0, 6.0)
	Dade® Innovin®	8.4 (3.6)	6.2 (0.0, 12.0)
aPTT	STA®-PTTa	89.8 (23.4)	96.0 (48.0, 144.2[b])
	HemosIL® SynthASil	23.1 (13.8)	18.0 (6.1, 48.0)
	Dade® Actin® FSL	48.4 (28.9)	48.0 (6.4, 119.8)
	TriniCLOT™ aPTT HS	42.8 (23.7)	48.0 (6.4, 96.0)

Abbreviations: Max, Maximum; Min, Minimum; SD, Standard Deviation.

[a]Time-to-resolution was defined as the first time post baseline following the start of oritavancin infusion that a test value returned to either the normal reference range (PT) or to the maximum of baseline or the normal reference range after elevation (aPTT).

[b]STA®-PTTa assay was not conducted for 1 subject at 120 h but an unscheduled assessment at 144.2 h was performed: aPTT was 36.6 sec and was within the normal reference range of the assay (39 sec).

Table 3. The maximum time-to-resolution of test interference varies amongst coagulation tests determined in subjects administered a single 1200 mg dose of oritavancin in the phase 1 study.

Coagulation test	Maximum time-to-resolution[a] (h)
Phospholipid-dependent	
PT/INR	12
aPTT	120
ACT	24
SCT	18
DRVVT	72
APCR	unaffected
Phospholipid-independent	
Anti-factor Xa	unaffected
TT	unaffected
Anti-Heparin-PF4	unaffected

[a]The maximum time-to-resolution indicated represents the time point at which 90% of subjects reached resolution (P90) of the affected coagulation test.

Conclusions

- A single dose of oritavancin was associated with falsely elevated values of some phospholipid-dependent coagulation tests. The extent of test elevations was concentration-dependent, as demonstrated in in vitro studies using oritavancin-spiked samples (Table 1).
- Oritavancin plasma concentrations following a single 1200 mg dose in subjects in this study are comparable to those in patients with ABSSSI (Figure 1). Thus, the estimates of time to resolution of potential lab test interference in normal subjects is expected to match those in infected patients.
- A relationship between oritavancin plasma concentrations and increases in PT/INR or aPTT was observed in the phase 1 study (Figure 2).
- The estimates of maximum time to resolution of test interference (Table 3) provides information on how to avoid coagulation test interference following a single dose of oritavancin.

Disclosures

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