ORIGINAL RESEARCH ARTICLE

A Two-Dose Oritavancin Regimen Using Pharmacokinetic Estimation Analysis

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Abstract

Background Antibiotics for the treatment of complicated, multidrug-resistant Gram-positive infections are limited, especially when prolonged treatment is necessary. Oritavancin is approved for the treatment of serious skin infections as a 1200 mg single-dose regimen, but case reports describe supplemental doses given at weekly intervals ranging from 800 mg to 1200 mg.

Objective This study determined population pharmacokinetic estimates for a 1200 mg single dose with and without an 800 mg dose 1 week apart.

Methods A simulated oritavancin 1200 mg dose was infused over 3 h followed 7 days later by a simulated 800 mg dose infused over 3 h for pharmacokinetic estimation.

Results The oritavancin dosing displayed predictable linear pharmacokinetics and therapeutic concentrations. The total and free oritavancin concentrations remained above the susceptibility breakpoint (0.12 mg/L) for 8 weeks and 4.6 weeks, respectively, with the two-dose regimen. This was significantly greater than the single-dose regimen. This regimen also results in a greater area under the drug concentration–time curve (AUC) above the susceptibility breakpoint compared to the single-dose regimen ($p < 0.001$), and it maintains a high AUC:minimum inhibitory concentration (MIC) ratio against organisms with MICs up to 0.25 mg/L.

Conclusion These results along with the observational clinical reports of success and safety with this dosing scheme of 1200 mg followed by 800 mg 7 days later provide evidence for further evaluation of this approach when prolonged oritavancin treatment may be indicated.

Key Points

Therapeutic concentrations of a novel oritavancin dosing regimen of 1200 mg and 800 mg administered 7 days apart were assessed in a pharmacokinetic model.

This dosing regimen achieved oritavancin concentrations above the susceptibility breakpoint (0.12 mg/L) for 8 weeks, and maintained a high AUC:MIC ratio for efficacy against organisms with MICs up to 0.25 mg/L.

Along with the observational clinical reports of success and safety with this dosing scheme, this study provides evidence for further evaluation of this approach when prolonged oritavancin treatment may be indicated.

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1 Introduction

Despite the available antibiotic options for invasive, multidrug-resistant Gram-positive infections, the treatment remains challenging for clinicians. New antibiotics with activity against these organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* spp. (VRE), are being used, but limitations exist that prevent broad applications. A major issue is the continued difficulties involved in treating specific infection types such as bone and joint infections, bacteremia and endocarditis, and pneumonia, among others [1–3]. Additionally, prolonged duration of antibiotic treatment associated with these infection types introduces toxicity concerns with some treatment options [4–7]. Further, the pharmacokinetics of antibiotics in difficult-to-penetrate compartments, such as bone, have not been well studied in patients during long-term treatment [8].

The prolonged half-life of the new lipoglycopeptide antibiotics, such as oritavancin, make them attractive options for patients requiring intravenous management of complicated infections [9, 10]. These agents possess broad-spectrum Gram-positive activity, particularly for oritavancin, with activity

against both MRSA and VRE. Multidrug-resistant organisms continue to account for a significant percentage of complicated infection types, therefore reliable activity against these strains is an important characteristic.

Oritavancin is frequently used for acute bacterial skin and skin-structure infections (ABSSSI) in susceptible Gram-positive organisms. Although oritavancin demonstrated activity against vancomycin-susceptible *Entercococcus* spp. in the SOLO I and II clinical trials [11, 12], recent clinical data suggest that it has high effectiveness in complicated infections due to VRE [10, 13]. This is despite oritavancin not having a defined pharmacokinetic–pharmacodynamic target against VRE. Case reports of successful treatment with oritavancin in patients with complicated infections also suggest that this antibiotic has a place in therapy for prolonged use beyond the initial 1200 mg single dose.

For prolonged oritavancin treatment, clinicians have used a variety of dosing strategies. Doses are most reportedly given at weekly intervals and have ranged from 800 mg to 1200 mg. In this study, we used population pharmacokinetic estimates to simulate oritavancin concentrations following a 1200 mg single dose with and without subsequent 800 mg dosing administered 1 week later. This study validates that 1200 mg followed by an 800 mg dose 7 days later prolongs targeted pharmacokinetic parameters for efficacy.

2 Methods

A simulation was performed to assess the predicted oritavancin concentrations that would result from doses of 1200 and 800 mg administered intravenously over 3 h 7 days apart. The population pharmacokinetic model used was based upon relatively sparse sampling (0, 3, 12, 24, 72, and 576 h) after a single 1200 mg intravenous dose of oritavancin infused over 3 h in 297 patients [14]. The covariate relationships included in the final simulation were median age and height based on the previously published pharmacokinetic model [14]. The model yielded similar parameters for a three-compartment model that was described by the same group in 2009 [15].

NONMEM (v7.4) was used to simulate total plasma concentrations for 500 hypothetical patients after a single 1200 mg intravenous dose over 3 h, as well as after doses of 1200 mg and 800 mg administered 1 week apart. The interindividual variances for the six pharmacokinetic parameters described for the three-compartment model by Rubino et al. were used, as were the additive and proportional residual errors. The NONMEM simulation also calculated both the cumulative time and the area under the drug concentration–time curve from zero to infinity [$AUC_{0-\infty}$ (mg·days/L)], during which the oritavancin concentration was above 0.12 mg/L. This threshold was used as it

is the lowest breakpoint for susceptibility for oritavancin among Gram-positive organisms. The results of the NONMEM simulations were processed using R (version 3.4.4) in RStudio (1.1.1335). A two-sided *t*-test was used to analyze the pharmacokinetic results between the single-dose and two-dose regimens with $p \leq 0.05$ for significance.

3 Results

An oritavancin 1200 mg dose infused over 3 h followed 7 days later by an 800 mg dose infused over 3 h displayed predictable and therapeutic concentrations. Figure 1 compares the simulated plasma oritavancin concentrations following one versus two doses. The blue and red lines show the median concentrations expected after one 1200 mg dose or two doses of 1200 mg and 800 mg, respectively. Similarly, the blue and red ribbons show the respective 90% confidence intervals for the two dosing regimens, with purple representing the overlap intervals between the regimens.

Table 1 displays the pharmacokinetic parameters achieved with the single- and two-dose regimens. The simulated $AUC_{0-72\,h}$ for total drug exposure after the single 1200 mg dose were 778.7, 1399.1, and 2481.4 (mg·h/L) for the fifth, 50th, and 95th percentiles, respectively. These percentiles were within 2.2–14.4% difference versus those determined by Rubino et al. with a similar 1200 mg dose simulation, corroborating the model consistency [14]. As expected, the second 800 mg dose provides slightly lower but overall similar maximum concentrations (C_{max}) versus the initial 1200 mg dose, and the minimum concentration (C_{min}) total and unbound free drug concentrations were significantly higher at day 29 with the two-dose regimen. Also, the $AUC_{0-\infty}$ was predictably 67% higher with the two-dose regimen over the estimation duration. The oritavancin concentrations remained above the susceptibility breakpoint (0.12 mg/L) with the two-dose regimen for the entire 8-week simulation for total drug and 4.6 weeks for unbound free drug. Compared to the single 1200 mg dose, the two-dose regimen provided oritavancin concentrations above the susceptibility breakpoint for 11.3 more days ($p < 0.0001$). The two-dose regimen simulated in our study provides a total drug AUC/minimum inhibitory concentration (MIC) $\geq 17,568$ (free unbound $> 2,635.2$) against organisms with an MIC value up to 0.25 mg/L.

4 Discussion

Oritavancin is increasingly used for a broad spectrum of Gram-positive pathogens and more complicated infections other than ABSSSI [13, 16]. The established safety profile of oritavancin despite the prolonged half-life has
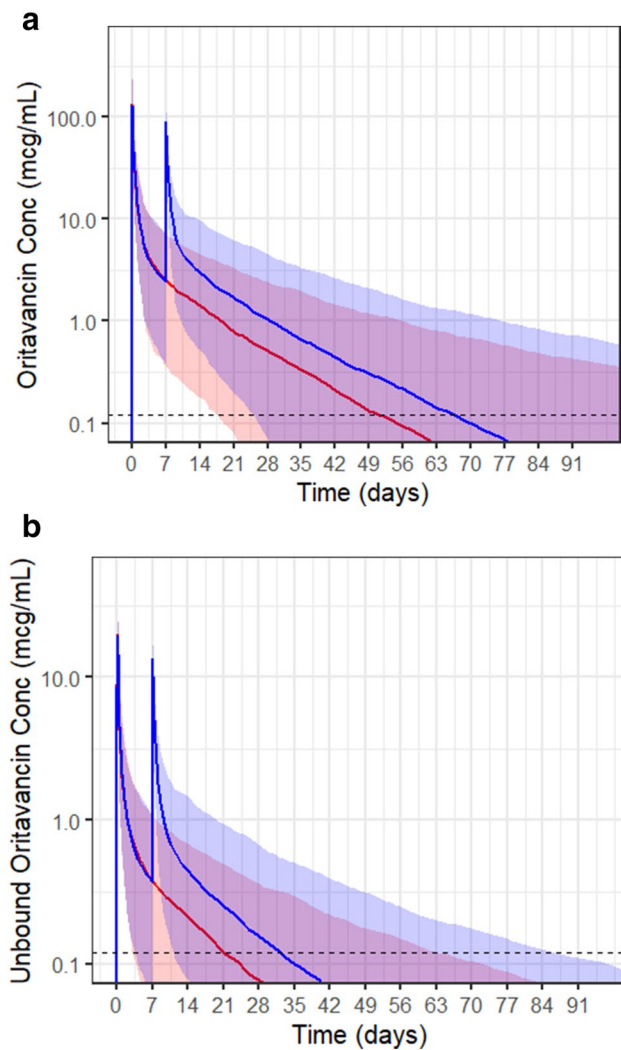
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Fig. 1 Comparison of simulated oritavancin concentrations. **a** Total oritavancin concentrations, **b** unbound free oritavancin concentrations. The blue line displays the median plasma concentrations expected after one 1200 mg dose followed by an 800 mg dose 1 week apart, and the red line represents the single 1200 mg dose. The ribbons represent the 90% confidence intervals, with purple ribbons representing overlap between the dosing schemes

Table 1 Comparison of key pharmacokinetic parameters in the simulated oritavancin exposures

Parameter[a]	1200 mg Day 1	1200 mg Day 1 800 mg Day 8
C_{max} (mg/L)		
Total drug	132.7 (69.8–244.8)	130.5 (63.2–236.1)
Unbound free drug[b]	19.9 (10.5–36.7)	19.6 (9.5–35.4)
C_{min} (mg/L) at Day 29		
Total drug	(0.02–2.46)	1.00* (0.07–4.50)
Unbound free drug[b]	0.08 (0.003–0.37)	0.16* (0.01–0.68)
Time above 0.12 mg/L (days)[b]	20.9 (3.1–63.1)	32.2* (7.9–85.8)
AUC while above 0.12 mg/L (mg·days/L)[b]	14.7 (5.9–35.8)	26.2* (9.9–61.2)

AUC area under the concentration–time curve, C_{max} maximum concentration, C_{min} minimum concentration

*Statistically different between dosing strategies ($p < 0.0001$, two-sided t-test)

[a]Values are median and (90% confidence interval)

[b]Concentration is of unbound oritavancin, calculated as total drug·0.15, where it is assumed that the protein-binding of oritavancin is 85% [24]

et al. study along with patients in a previous study by this group [13] received a full 1200 mg dose, often at day 10, if the second dose was not administered within 7 days. This dosing scheme was not analyzed in our study but should be considered for future work.

SIMPLIFI was a multicenter, randomized, double-blind, phase II clinical trial evaluating the safety and effectiveness of oritavancin in complicated skin and skin structure infections. It compared three different oritavancin dosing regimens: daily—200 mg for 3–7 days; infrequent—800 mg on day 1 with the option for 400 mg on day 5; single 1,200 mg dose. In the intent-to-treat groups clinical cure/improvement was similar; 72.4% in the daily-dose group, 78.2% in the infrequent group, and 81.1% in single-dose group. Oritavancin was well tolerated—most adverse events were mild or moderate, and more than half were unrelated to study treatment [18, 19]. This study did not evaluate pharmacokinetics; however, it does support the safety of oritavancin at different doses and frequency, as well as efficacy.

The previous oritavancin pharmacokinetic studies by Rubino et al. used data from two separate populations: (1) healthy subjects and patients with complicated skin and skin structure infections and bacteremia receiving fixed and weight-based dosing ranges [14], and (2) SOLO I and II patients with ABSSSI receiving a single 1200 mg dose [11, 12]. With our study of the novel 800 mg second dose, the C_{max} was similar to the "loading dose" of 1200 mg, indicating that this regimen will achieve similar pharmacokinetic parameters. Furthermore, when comparing drug exposures,

stimulated clinical experimentation with use and dosing strategies. Along with initial case reports of use in complicated infection types, the studies in this supplement demonstrate more evidence of the favorable safety, effectiveness, and pharmacoeconomics of oritavancin treatment. In a retrospective study by Brownell et al., most of the 75 patients received an initial 1200 mg dose followed by 1200 mg or 800 mg weekly thereafter, resulting in cure or improvement in 93% of these patients [17]. Our pharmacokinetic simulation of 1200 mg and 800 mg doses administered 7 days apart support this novel dosing approach when more than a single dose is used for infection treatment. It should be noted that some patients in the Brownell

the median AUC while above 0.12 mg/L in our study was similar to $AUC_{0-\infty}$ for the single 1200 mg dose (110 mg·days/L vs. ~ 117 mg·days/L). However, the 1200 mg and 800 mg doses 1 week apart in our study resulted in a total drug AUC while above 0.12 mg/L of 183.5 mg·days/L and unbound free drug of 26.2 mg·days/L. Based on animal models of infection, the antimicrobial activity of oritavancin appears to correlate with the ratio of $AUC_{0-72\ h}$/MIC [20]. This is consistent with lipoglycopeptide antibiotics such as vancomycin and daptomycin [21, 22]. In preliminary analysis of clinical studies assessing pharmacokinetic target attainment, AUC/MIC > 17,568 appears to be associated with clinical response in patients [23]. In our study, this AUC was achieved in organisms above the susceptibility breakpoint with MICs up to 0.25 mg/L. Future pharmacokinetic studies may indicate the target attainment and pharmacokinetic parameters with additional 800 mg doses.

Schulz et al. described the 800 mg dosage using estimated pharmacokinetic linear assumptions, and overall the clinical outcomes were promising [13]. However, the two-thirds (800 mg) supplemental weekly-dosing approach has not been validated by pharmacokinetic modeling, which could help inform clinicians' use of this approach.

5 Conclusion

This population pharmacokinetic estimate analysis provides evidence that 1200 mg and 800 mg doses 1 week apart achieve appropriate oritavancin concentrations with serum levels above the susceptibility breakpoint of 0.12 mg/L for over 4 weeks, which is approximately 11 days longer than the 1200 mg single-dose simulation. When prolonged treatment is required, our analysis suggests pharmacokinetic advantages over single-dose treatment with this regimen. Combined with previous reports of the clinical success and safety of this dosing scheme, our analysis further validates use of this dosing when prolonged oritavancin treatment is desired [13]. Additional modeling is needed for multiple supplemental doses as well as in tertiary compartments such as bone and deep tissue to further understand novel oritavancin treatment approaches.

Compliance With Ethical Standards

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