A-009

Pharmacodynamics of single dose Oritavancin against *Staphylococcus aureus*

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Amended Abstract

Background:
Oritavancin (ORI) is a semi-synthetic lipoglycopeptide with potent in vitro bactericidal activity against S. aureus. Its PK-PD properties allow it to be given as single dose therapy in skin infection. For this reason, it is important to establish the exposure response relationship for ORI over prolonged time courses of drug exposures. Such experiments are difficult to perform in vivo but in vitro pharmacokinetic (PK) models offer a flexible platform in studying drug exposure over several days. We used such an in vitro PK model to study the PD of single dose exposures of ORI against S. aureus over 96h.

Methods:
7 strains of S. aureus (all MRSA) were used with oritavancin MIC of 0.12 (n=5), MIC 0.25 (n=1), MIC 0.5mg/L(n=1). A dilutional in vitro model using polypropylene bottles was used to simulate a range of AUC/MIC ratios. ORI was infused over 3h at time zero. Simulations were performed over 96h. Antibacterial effect (ABE) was measured by log change at 24h (d24h) (log CFU/mL), 48h (d48h), 72h (d72h) and 96h (d96h) compared to the initial inoculum. The initial inoculum was 10^6 CFU/mL. AUC/MIC was related to ABE, i.e. AUC24/MIC to d24, AUC48/MIC to d48, etc.

Results:
In all simulations with an ORI Cmax 20mg/L – modelling free drug associated with a 1200mg dose– there was rapid killing and no regrowth. The mean AUC/MIC for stasis or -1 log, -2 log or -3 log reductions in viable count at 24h, 48h, 72h and 96h are shown below.ORI was cidal versus all S. aureus strains with the AUC/MIC for -3 log reduction in count compared to initial inoculum being 2-3 fold greater than that for static effect. The AUC/MIC increased for each antibacterial effect over time, being 8-10 times greater at 96h than at 24h. The two strains with higher ORI MICs had similar AUC/MIC to ABE response characteristics to those with lower MICs.

	ABE			
	Static effect	-1 log drop	-2 log drop	-3 log drop
AUC 24/MIC vs d24h	14.2	17.9	22.919.1	28.7
AUC 48/MIC vs d48h	34.7	50.7	61.9	87.6
AUC 72/MIC vs d72h	53.5	62.7	72.6	93.7
AUC 96/MIC vs d96h	111.8	137.1	163.4	217.2

Conclusion:
Free drug ORI concentrations associated with a single 1200 mg dose produced rapid clearance of S. aureus strains from an in vitro model of infection. AUC/MIC for ABE varied over time and also with static or cidal endpoints.

Introduction

- Oritavancin (ORI) is a semi synthetic lipoglycopeptide with broad activity against Gm-positive pathogens; its mode of action involves inhibition of cell-wall synthesis.
- ORI is rapidly bactericidal against MRSA and MSSA strains at pharmacokinetic relevant concentrations – i.e. 0.5-16mg/L.
- The MIC90 for ORI against staphylococci is ≤0.25mg/L, against hVISA, VISA and VRSA, the MIC90 are in the range 0.5-2mg/L.[1]
- Population PK modelling shows that 1200 mg ORI administered over 3h produced a Cmax of 129mg/L, an 0-24h AUC of 854mg/L, an alpha phase half life of 2.0h, beta phase half-life of 31h and a gamma phase half life of 393h.[2] Protein binding is approx 85% in man and other species.[3]
- In neutropaenic mouse thigh infection (NMTI) models, Cmax was strongly correlated with antibacterial effect (ABE) for a single strain of S. aureus. Further NMTI model studies have indicated that a 1200mg single dose was more effective than 400mg ORI once daily for three days.[4]
- Human PD analyses have been less informative; neither AUC24/MIC, Cmax/MIC nor fT>MIC could be convincingly related to outcome in daily-dosing studies conducted to date.

The objective of this study was to establish the Cmax/MIC, AUC/MIC and AUC, ABE relationship at 24h, 48h, 72h and 96h for S. aureus using a dose ranging study based on free drug serum concentrations associated with an ORI 1200mg dose.

Materials and methods

- 100% MHB plus 0.01% polysorbate was used for all experiments.
- A dilutional *in vitro* pK using polypropylene bottles was used to simulate a range of ORI *f*Cmax concentrations 20, 10, 5, 1.0, 0.5, 0.25mg/L and 0mg/L infused over 3h.
- ORI concentrations were confirmed using bioassay methodology. The limit of detection was 1mg/L.
- Seven strains of MRSA (including one MRSA-hVISA) with ORO MICs in the range 0.12-0.5mg/L were utilised. The inoculum was 10^6cfu/mL and experiments were conducted over 96h. Change in population profile was determined by broth micro-dilution MICs on survivors at 96h.The limit of detection was 2 x10^2 cfu/mL.
- ABE measured by log change in viable count at 24h, 48h, 72h and 96h was correlated to *f*Cmax/MIC, *f*AUC/MIC, *f*AUC and the average *f*AUC24h using a sigmoid Emax equation.

Results

- ORI, vancomycin, oxacillin and daptomycin MICs for the *S. aureus* strains tested are shown in Table 1. At the standard 1200mg dose (*f*Cmax 20mg/L) rapid bacterial killing was observed with all strains-viable counts were below the limit of detection at 3-4h. No re-growth was seen.

Table I: ORI, vancomycin, oxacillin and daptomycin MICs

Strain Reference	MIC (mg/L)			
	Oritavancin	Vancomycin	Oxacillin	Daptomycin
46951	0.12	1	32	1
45796	0.12	1	128	2
36895	0.12	1	128	0.5
43456	0.12	1	128	0.5
31236	0.12	1	8	0.5
45800	0.25	1	128	1
45798	0.5	2	>128	8

Table 2:*f*Cmax/MIC required for a static, one and two log reduction in viable count at 24h

Strain	MIC (mg/L)	static	-1log drop	-2log drop	-3log drop
46951	0.12	4.5	4.5	4.5	4.5
45796	0.12	3.4	4.5	6.7	12.3
36895	0.12	1.1	1.1	1.1	1.1
43456	0.12	1.1	2.2	3.4	5.0
31236	0.12	0.6	0.6	0.6	0.6
45800	0.25	3.1	3.5	4.0	4.1
45798*	0.5	1.8	1.6	1.8	2.4
Mean		2.2±1.5	2.6±1.6	3.2±2.2	4.3±3.9

Table 3: *f*Cmax/MIC required for a static, one and two log reduction in viable count at 96h

Strain	MIC (mg/L)	static	-1log drop	-2log drop	-3log drop
46951	0.12	13.4	14.5	15.7	17.9
45796	0.12	8.9	8.9	8.9	10.2
36895	0.12	7.8	9.0	9.0	10.1
43456	0.12	4.0	4.0	4.0	4.0
31236	0.12	3.5	4.7	5.9	7.6
45800	0.25	3.8	4.0	4.0	4.3
45798*	0.5	12.2	13.0	13.8	15.5
Mean		7.7±4.1	8.3±4.3	8.8±4.6	9.9±5.3

Table 4: *f*AUC24/MIC required for a static, one and two log reduction in viable count at 24h

strain	MIC (mg/L)	static	-1log drop	-2log drop	-3log drop
46951	0.12	22.0	36.6	51.3	73.3
45796	0.12	27.0	29.2	29.2	29.3
36895	0.12	4.1	6.2	12.5	20.8
43456	0.12	4.9	10.4	17.4	29.2
31236	0.12	7.3	7.3	7.3	4.8
45800	0.25	24.5	26.3	28.1	28.1
45798*	0.5	11.8	13.4	18.6	22.2
Mean		14.5±9.8	18.5±12.0	23.5±14.6	29.7±21.1

*Meaned data

Results

- Figures 1-3 show the relationship between *f*Cmax/MIC, *f*AUC/MIC and *f*AUC with log reduction in viable count for all strains at 24h. *f*Cmax/MIC, *f*AUC/MIC and fAUC increased with time (Tables 2-7), and the 24h antibacterial endpoint is predictive of effect up to 96h for human dose simulations.
- The average daily *f*AUC/MIC was also related to change in viable count at 24h. The average daily *f*AUC/MIC for a 24h static, -1 log drop, -2 log drop were 4.38±3.3, 6.4±4.5 and 8.9±6.4 respectively. No emergence of resistance as indicated by an increased MIC was observed.
- We were unable to determine the dominant pD driver for oritavancin. However, PDI targets can be suggested for 24h antibacterial effects for *f*Cmax/MIC, *f*AUC/MIC and *f*AUC.
- Suggested PDI targets are *f*Cmax/MIC >3-5; *f*AUC/MIC>15-20; *f*AUC >6-10

Table 5: *f*AUC96/MIC required for a static, one and two log reduction in viable count at 96h

Strain	MIC (mg/L)	static	-1log drop	-2log drop	-3log drop
46951	0.12	358.8	463.2	565.8	720.4
45796	0.12	94.3	148.8	230.4	385.9
36895	0.12	70.0	75.8	90.4	99.2
43456	0.12	37.9	49.6	72.9	107.9
31236	0.12	40.8	46.7	58.3	67.1
45800	0.25	33.1	40.7	42.3	45.3
45798*	0.5	129.9	136.0	142.0	156.0
Mean		109.3±115.5	137.3±150.2	171.73±185.1	226.0±245.9

Table 6: *f*AUC24 required for a static, one and two log reduction in viable count at 24h

Strain	MIC (mg/L)	static	-1log drop	-2log drop	-3log drop
46951	0.12	3.0	3.2	3.4	3.4
45796	0.12	2.2	3.3	5.3	9.9
36895	0.12	0.8	1.0	1.7	2.6
43456	0.12	1.0	1.4	2.4	3.6
31236	0.12	0.4	0.8	0.8	1.2
45800	0.25	5.1	5.5	6.3	6.9
45798*	0.5	4.5	5.3	6.0	7.3
Mean		2.4±1.9	2.9±2.0	3.7±2.2	5.0±3.1

Table 7: *f*AUC96 required for a static, one and two log reduction in viable count at 96h

Strain	MIC (mg/L)	static	-1log drop	-2log drop	-3log drop
46951	0.12	44.3	57.6	69.2	89.1
45796	0.12	9.8	10.3	10.4	10.9
36895	0.12	7.2	7.8	8.7	10.1
43456	0.12	4.7	4.8	5.3	5.4
31236	0.12	4.9	6.1	7.2	8.6
45800	0.25	9.8	10.2	10.2	10.9
45798*	0.5	19.2	21.8	26.0	31.7
Mean		14.3±14.1	16.9±18.8	19.9±22.9	23.8±30.1

Figure1. Relationship between Cmax/MIC and log reduction in viable count at 24h (all strains)

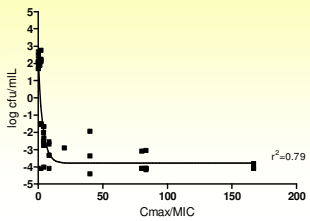


Figure 2: Relationship between AUC/MIC and log reduction in viable count at 24h (all strains)

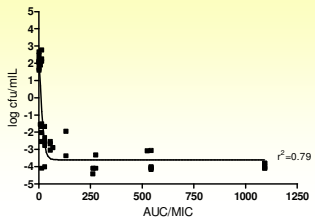
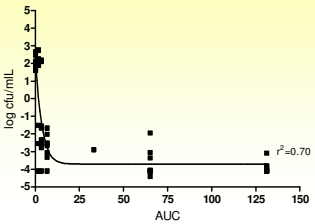


Figure 3: relationship between AUC and log reduction in viable count at 24h (all strains)



Conclusions

- This series of experiments clearly showed an ORI exposure response relationship for *f*Cmax/MIC, *f*AUC/MIC and *f*AUC against *S. aureus*.
- They confirm the marked and sustained bactericidal action of ORI at simulations of human free drug concentrations associated with a dose of 1200mg over 4 days.

References
1.Mendes et al. Clin Infect Dis. 2012 Apr;54 Suppl 3:S203-13; 2. Belley et al. Antimicrob Agents Chemother. 2013 Jan;57(1):205-1; 3. Arhin et al. Antimicrob Agent Chemother .2010 54, 3481-3483; 4. Ambrose et al. Clin Infect Dis. 2012 Apr;54 Suppl 3:S220-8.

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