

THE EFFECT OF LUNG SURFACTANT ON THE IN VITRO ACTIVITY OF DALBAVANCIN AGAINST STAPHYLOCOCCUS AUREUS AND STREPTOCOCCUS PNEUMONIAE

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ABSTRACT

Background: Dalbavancin is a long acting intravenous lipoglycopeptide antibiotic with activity against Gram positive organisms that is currently in Phase III clinical studies for acute bacterial skin and skin structure infection. For potential respiratory infection indication purposes, this study was performed to determine the effect of lung surfactant on the in vitro activity of dalbavancin against *S. aureus* and *S. pneumoniae*.

Methods: A total of 5 *S. aureus* and 5 *S. pneumoniae* were tested by CLSI broth microdilution (BMD) methods for dalbavancin with and without the addition of 1% and 5% lung surfactant (Survanta®—extract of bovine lung surfactant consisting of 89.3% phospholipids, 7.1% other lipids and 5–10% protein). Daptomycin was also tested for *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619, as a positive control.

Results: Dalbavancin MIC results for broth+ surfactant in comparison to broth only:

Species	1% Surfactant	5% Surfactant
<i>S. aureus</i>	Equivalent MIC for 4 strains 1 dilution higher MIC for 1 strain	1 dilution higher MIC for 5 strains
<i>S. pneumoniae</i>	Equivalent MIC for 3 strains 1 dilution higher MIC for 2 strains	1 dilution higher MIC for 5 strains

In contrast, daptomycin MICs for *S. aureus* ATCC 29213 were 5 and 7 dilutions higher with addition of 1% and 5% surfactant, respectively and for *S. pneumoniae* ATCC 49619 were 3–4 dilutions and 6 dilutions higher with addition of 1% and 5% surfactant respectively.

Conclusion: The addition of lung surfactant did not have a significant impact on the in vitro susceptibility of *S. aureus* and *S. pneumoniae* to dalbavancin as determined by broth microdilution.

INTRODUCTION

This study was performed in order to evaluate the in vitro activity of dalbavancin against *S. aureus* and *S. pneumoniae* in the presence of lung surfactant for purposes of a potential respiratory indication. Higher MIC results in the presence of surfactant were obtained for daptomycin in a similar in vitro model and in the case of daptomycin, accurately correlated with the failure of daptomycin in clinical CAP and animal pulmonary infection models.¹ Daptomycin was tested in the current study as a positive control.

METHODS

Antimicrobial Agents

- Dalbavancin (0.008–8 mcg/mL)
- Daptomycin (0.03–32 mcg/mL)

Bacterial Strains

- The strain list is shown in Table 1. *S. aureus* stock strains were selected to include 2 methicillin susceptible (MSSA), 2 methicillin resistant (MRSA) and 1 vancomycin intermediate (VISA). *S. pneumoniae* stock strains were selected to include 2 penicillin susceptible (PSSP), 1 penicillin intermediate (PISP) and 2 penicillin resistant (PRSP).

Lung Surfactant

- Survanta®—extract of bovine lung surfactant consisting of 89.3% phospholipids, 7.1% other lipids and 3.6% protein. Composition varies slightly in human lung surfactant (80–85% phospholipids), 10% other lipids and 5–10% protein).²

Susceptibility Method^{3,4}

- Dalbavancin—CLSI broth microdilution in cation adjusted Mueller Hinton with addition of 0.002% polysorbate 80 (P80) and also tested with addition of 1% and 5% Survanta®. Each strain was tested one time using each media type.
- Daptomycin—CLSI broth microdilution in Mueller Hinton containing 50 mcg/mL calcium and also tested with addition of 1% and 5% Survanta®. *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619 were tested four times using each media type.

RESULTS

Table 1. Dalbavancin Broth Microdilution MICs with 1% and 5% Surfactant Concentrations Compared to Standard MICs (mcg/mL) for 5 *S. aureus* and 5 *S. pneumoniae*

LSI Reference #	Resistance Type	MIC (mcg/mL)		
		CAMHB*	+1% Survanta	+5% Survanta
<i>Staphylococcus aureus</i>				
SA ATCC 29213	MSSA, CLSI MIC QC strain	0.06	0.06	0.12
SA ATCC 25923	MSSA, CLSI Disk QC strain	0.06	0.06	0.12
SA ATCC 700699 (Mu50)	VISA	1	1	2
G322-001SA	MRSA	0.03	0.06	0.06
G322-002SA	MRSA	0.5	0.5	1
<i>Streptococcus pneumoniae</i>				
SA ATCC 49619	PSSP, CLSI MIC QC strain	0.015	0.015	0.03
G322-019SP	PSSP	0.015	0.03	0.03
G322-023SP	PISP	0.015	0.03	0.03
G322-029SP	PRSP	0.015	0.015	0.03
G322-030SP	PRSP	0.015	0.015	0.03

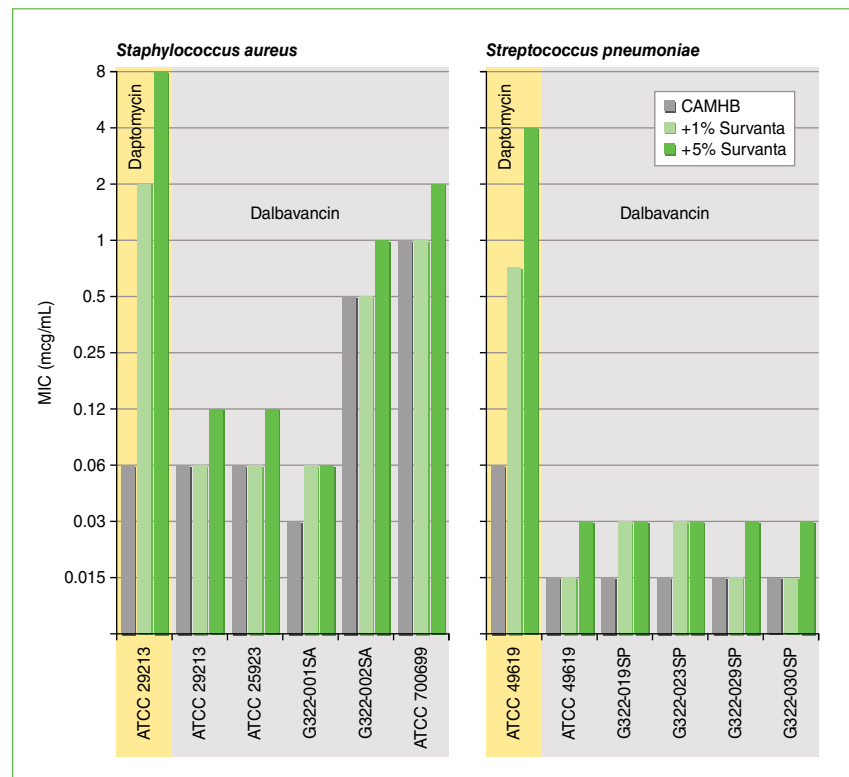
*5% Lysed horse blood added for *S. pneumoniae*

Table 2. Daptomycin Broth Microdilution MICs (4 replicates) with 1% and 5% Surfactant Concentrations Compared to Standard MICs (mcg/mL) for *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619

LSI Reference #	CAMHB*	MIC (mcg/mL)	
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SA ATCC 29213	0.06, 0.06, 0.06, 0.06	2, 2, 2, 2	8, 8, 8, 8
SP ATCC 49619	0.06, 0.06, 0.06, 0.06	1, 0.5, 0.5, 1	4, 4, 4, 4

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Figure 1. Dalbavancin Broth Microdilution MICs with 1% and 5% Surfactant Concentrations Compared to Standard MICs (mcg/mL)



- Dalbavancin *S. aureus* MICs were identical for 4 strains and 1 dilution higher for 1 strain in the presence of 1% Survanta compared to broth only MICs.
- Dalbavancin *S. aureus* MICs were 1 dilution higher for 5 strains in the presence of 5% Survanta compared to broth only MICs.
- Dalbavancin *S. pneumoniae* MICs were identical for 3 strains and 1 dilution higher for 2 strains in the presence of 1% Survanta compared to broth only MICs.
- Dalbavancin *S. pneumoniae* MICs were 1 dilution higher for 5 strains in the presence of 5% Survanta compared to broth only MICs.
- Daptomycin *S. aureus* ATCC 29213 MICs were 5 dilutions higher in the presence of 1% Survanta and 7 dilutions higher in the presence of 5% Survanta compared to broth only MICs.
- Daptomycin *S. pneumoniae* ATCC 49619 MICs were 3–4 dilutions higher in the presence of 1% Survanta and 6 dilutions higher in the presence of 5% Survanta compared to broth only MICs.

CONCLUSIONS

- Dalbavancin MICs for CAMHB and for CAMHB +1% and 5% surfactant were similar (within expected ± 1 dilution) for *S. aureus* and *S. pneumoniae*.
- In contrast, daptomycin MICs were significantly impacted (3–7 dilutions higher) by the presence of surfactant.
- Although this in vitro model does not perfectly depict natural surfactant [i.e. bovine source and protein levels slightly lower than adult lung tissue⁴], there is no indication that dalbavancin activity in human lung infection will be negatively impacted.

REFERENCES

- Silverman JA, Mortin LI, Vanpraagh AD, Li T, Alder J. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *J Infect Dis.* 2005 Jun 15; 191(12):2149-52.
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1622

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®Survanta [(beractant) Intratracheal Suspension Bovine Pulmonary Surfactant] is a registered trademark of Abbott Laboratories, Inc.

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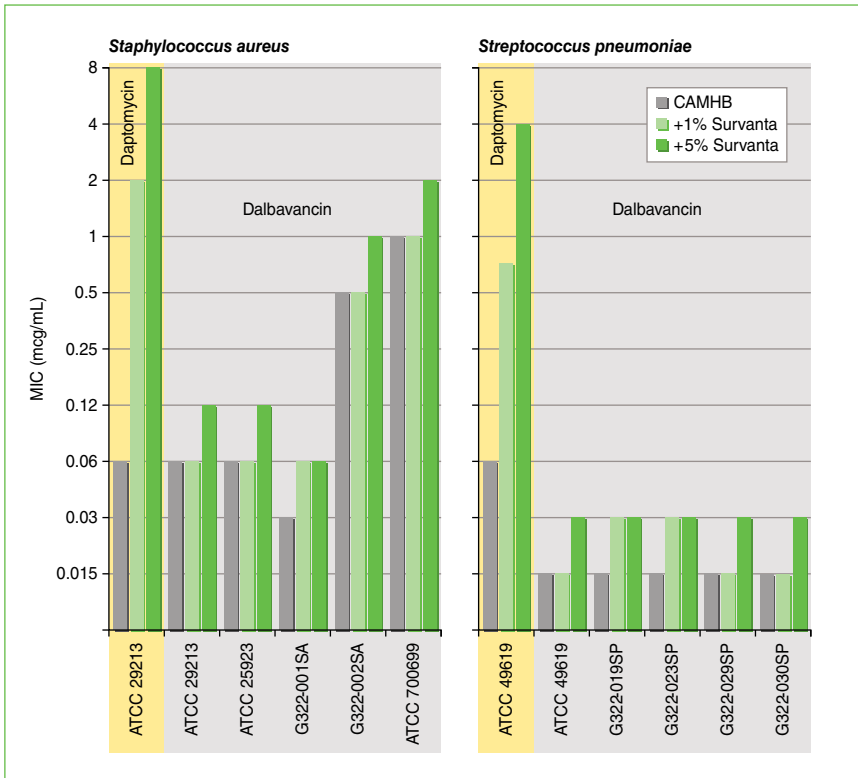
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