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Daptomycin *in vitro* activity tested against 2,221 Gram-positive strains collected from European hospitals (2002)

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ABSTRACT

Background: Daptomycin (DAP) is a cyclic lipopeptide recently approved by the US FDA for the treatment of complicated skin and skin structure infections. We evaluated the contemporary *in vitro* activity of DAP against a collection of Gram-positive (GP) strains collected in European medical centers in 2002.

Methods: 2,221 clinical GP strains were collected from 29 centers. The collection included *S. aureus* (763 strains; 31% oxacillin [OXA]-resistant [R]); coagulase-negative staphylococci (CoNS; 281 strains; 79% OXA-R), enterococci (260; 4% vancomycin [VAN]-R), streptococci (904 strains) and other GP species (13 strains). The strains were tested using NCCLS broth microdilution in Mueller-Hinton broth with 50 mg/L Ca^{2+} against DAP. More than 20 comparators were also tested.

Results: DAP inhibited all tested strains at ≤4 mg/L and only the enterococcal isolates showed DAP MICs of 4 mg/L (14 strains; 5.4%). All staphylococcal and streptococcal isolates were inhibited at ≤1 mg/L of DAP. The activities of DAP, VAN, teicoplanin (TEI), quinupristin/dalfopristin (Q/D) and linezolid (LZD) are shown in the table:

Organism (no. tested)	MIC_{90} (mg/L) / % susceptible				
	DAP	VAN	TEI	Q/D	LZD
S. aureus (763)	0.5/100	1/100	1/100	0.5/100	2/100
CoNS (281)	0.5/-	2/100	4/98	0.5/99	1/100
S. pneumoniae (SPN; 746)	0.25/-	0.5/100	0.5/-	0.5/100	1/100
β-haemolytic streptococci (75)	≤0.12/-	0.5/100	≤0.12/-	0.5/100	1/100
viridans group streptococci (77)	0.25/-	1/100	≤0.12/-	1/100	1/100
E. faecalis (EF; 192)	2/100	2/97	1/97	>8/1	2/100
E. faecium (EFM; 57)	4/-	2/91	2/93	2/79	2/100

Conclusions: DAP was active against enterococci irrespective of VAN-R and Q/D-R and also against PEN-R SPN. DAP showed a significant potency and spectrum against all GP organisms including multi-drug resistant strains and may represent a therapeutic option for infections caused by these pathogens.

INTRODUCTION

Daptomycin (formerly LY146032) is a novel cyclic lipopeptide antibiotic naturally produced by *Streptomyces roseosporus*. Daptomycin acts by inserting into the bacterial cytoplasmic membrane in a calcium-dependent fashion. Daptomycin binds to bacterial membranes and causes a rapid depolarization of membrane potential. The loss of membrane potential leads to inhibition of protein, DNA and RNA synthesis which results in rapid bacterial cell death.[1] This mechanism of action is novel compared to classes of antimicrobial agents currently marketed and no cross-resistance with other drug classes has been demonstrated.

Daptomycin displays linear pharmacokinetics, long half-life (8-9 h) and high protein binding (92%), that allow for once daily dosing.[2] This compound (4 mg/kg IV q 24 h) showed similar results to both vancomycin (1 g IV q 12 h) or semi-synthetic penicillins (i.e. nafcillin, oxacillin, cloxacillin, or fluclox-acillin; 4-12 g IV per day) for the treatment of complicated skin and skin structure infection.

Daptomycin has shown potent *in vitro* activity against most Gram-positive bacterial species and its spectrum includes multi-drug resistant strains for which there are very few therapeutic alternatives, such as vancomycin-resistant enterococci (VRE), methicillin-resistant staphylococci (MRSA), and penicillin-resistant streptococci.[3] In the present study we evaluated the *in vitro* activity of daptomycin against contemporary clinical strains collected in European medical centers.

MATERIALS AND METHODS

Bacterial isolates

A total of 2,221 clinical Gram-positive strains were collected in 2002 from 29 medical centers located in 14 countries: France (six centers), Germany (four), Italy (three), Spain (three), United Kingdom (three), Turkey (two), Belgium (one), Greece (one), Ireland (one), Israel (one), Poland (one) Russia (one), Sweden (one) and Switzerland (one). The collection included *Staphylococcus aureus* (763 strains; 31.1% oxacillin-resistant); coagulase-negative staphylococci (281 stains; 79.0% oxacillin-resistant), *Enterococcus faecalis* (192 strains; 2.6% vancomycin-resistant), *Enterococcus faecium* (57 strains; 7.0% vancomycin-resistant), *Enterococcus* spp. (11 strains), β-haemolytic streptococci (75 strains); viridans group streptococci (77 strains; 24.7% penicillin-nonsusceptible), *Streptococcus pneumoniae* (746 strains; 27.6% penicillin-non-susceptible), *Streptococcus bovis* (six strains) and other Gram-positive species (13 strains). The pathogens were non-duplicate clinical isolates collected from bloodstream, respiratory tract, skin and soft tissue and urinary tract infections.

Susceptibility testing

The strains were tested according to the National Committee for Clinical Laboratory Standards (NCCLS) M7-A6 broth microdilution methods.[4] Daptomycin and more than 20 comparator agents were tested in dry-form microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, OH). The test medium was Mueller-Hinton broth adjusted to contain physiologic levels of calcium (50 mg/L) for testing daptomycin.[5] Susceptibility was defined according to NCCLS interpretive criteria.[6] Daptomycin susceptible breakpoints of ≤1 and ≤4 mg/L were used for *S. aureus* and vancomycin-susceptible *E. faecalis*, respectively, as recently approved by the Food and Drug Administration (FDA). The FDA also approved a breakpoint of ≤1 mg/L for some β-haemolytic streptococcal species, while no breakpoints have been established by the NCCLS or FDA for other organisms evaluated in the present study. The following quality control organisms were tested weekly: *S. pneumoniae* ATCC strain 49619, *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213.

Table. ***In vitro*** **activity of daptomycin and comparator drugs tested against Gram-positive clinical strains collected from European hospitals (SENTRY, 2002)**

Organism/antimicrobial agent (no. tested)		MIC (mg/L)			% by category:	
		50%	90%	Range	Susceptible	Resistant
S. aureus	**Daptomycin[a]**	**0.25**	**0.5**	**≤0.12-1**	**100**	**0.0**
Oxacillin-susceptible (526)	Oxacillin	0.5	1	≤0.06-2	100	0.0
	Vancomycin	1	1	0.25-2	100	0.0
	Teicoplanin	≤2	≤2	≤2-4	100	0.0
	Quinupristin/Dalfopristin	≤0.25	0.5	≤0.25-1	100	0.0
	Linezolid	2	2	0.5-4	100	-[b]
S. aureus	**Daptomycin[a]**	**0.25**	**0.5**	**≤0.12-1**	**100**	**0.0**
Oxacillin-resistant (237)	Oxacillin	>8	>8	4->8	0.0	100
	Vancomycin	1	2	0.5-2	100	0.0
	Teicoplanin	≤2	≤2	≤2-16	99.2	0.0
	Quinupristin/Dalfopristin	0.5	0.5	≤0.25->8	97.9	1.7
	Linezolid	2	2	0.5-2	100	-[b]
Coagulase-negative	**Daptomycin[a]**	**0.25**	**0.5**	**≤0.12-1**	-[b]	-[b]
staphylococci (281)	Oxacillin	8	>8	≤0.06->8	21.0	79.0
	Vancomycin	1	2	0.5-2	100	0.0
	Teicoplanin	≤2	4	≤2->16	97.9	0.4
	Quinupristin/Dalfopristin	0.25	0.5	≤0.25->8	98.9	0.8
	Linezolid	1	1	≤0.25-2	100	0.0
E. faecalis	**Daptomycin[a]**	**1**	**2**	**0.25-4**	**100**	**0.0**
Vancomycin-susceptible (187)	Vancomycin	1	2	0.5-4	100	0.0
	Teicoplanin	≤2	≤2	≤2	100	0.0
	Quinupristin/Dalfopristin	8	>8	≤0.25->8	1.1	92.0
	Linezolid	2	2	0.5-2	100	0.0
E. faecalis	**Daptomycin[a]**	**1**	-	**0.25-1**	-[b]	-[b]
Vancomycin-resistant (5)	Vancomycin	>16	-	>16	0.0	100
	Teicoplanin	>16	-	>16	0.0	100
	Quinupristin/Dalfopristin	>8	-	8->8	0.0	100
	Linezolid	2	-	0.5-2	100	0.0
***E. faecium* (57)**	**Daptomycin[a]**	**2**	**4**	**≤0.12-4**	-[b]	-[b]
	Vancomycin	1	2	0.25->16	91.2	7.0
	Teicoplanin	≤2	≤2	≤2->16	93.0	7.0
	Quinupristin/Dalfopristin	1	2	0.25-8	65.0	3.4
	Linezolid	2	2	≤0.25-2	100	-
***Enterococcus* spp.[c] (11)**	**Daptomycin[a]**	**2**	**2**	**0.5-4**	-[b]	-[b]
	Vancomycin	1	4	0.5-4	100	0.0
	Teicoplanin	≤2	≤2	≤2-4	100	0.0
	Quinupristin/Dalfopristin	1	4	0.5-4	72.7	-
	Linezolid	2	2	0.5-2	100	0.0
β-haemolytic	**Daptomycin[a]**	**≤0.12**	**0.25**	**≤0.12-0.5**	**100**	**0.0**
streptococci (75)	Penicillin	≤0.016	0.06	≤0.016-0.12	100	0.0
	Vancomycin	0.25	0.5	≤0.12-1	100	0.0
	Teicoplanin	≤2	≤2	≤2	-	-
	Quinupristin/Dalfopristin	0.25	0.5	≤0.25-1	100	0.0
	Linezolid	1	1	≤0.25-2	100	0.0
viridans group	**Daptomycin[a]**	**0.25**	**0.5**	**≤0.12-1**	-[b]	-[b]
streptococci (77)	Penicillin	0.06	1	≤0.016-8	75.3	5.2
	Vancomycin	0.5	1	≤0.12-1	100	0.0
	Teicoplanin	≤2	≤2	≤2	-	-
	Quinupristin/Dalfopristin	0.5	1	≤0.25-1	100	0.0
	Linezolid	1	1	≤0.25-2	100	0.0
***S. pneumoniae* (746)**	**Daptomycin[a]**	**≤0.12**	**0.25**	**≤0.12-1**	-[b]	-[b]
	Penicillin	≤0.03	2	≤0.03-4	72.4	13.7
	Vancomycin	0.25	0.5	≤0.06-2	100	0.0
	Teicoplanin	≤2	≤2	≤2-8	-	-
	Quinupristin/Dalfopristin	0.25	0.5	≤0.06-1	100	0.0
	Linezolid	1	1	≤0.25-2	100	0.0
***S. bovis* (6)**	**Daptomycin[a]**	**≤0.12**	-	**≤0.12**	-[b]	-[b]
	Penicillin	0.06	-	0.03-0.12	100	0.0
	Vancomycin	0.25	-	0.25-0.5	100	0.0
	Teicoplanin	≤0.12	-	≤0.12-0.25	100	0.0
	Quinupristin/Dalfopristin	0.5	-	0.12-1	100	0.0
	Linezolid	1	-	0.25-0.5	100	0.0

a. The FDA has recently approved susceptible breakpoints as follows: *S. aureus* (oxacillin-susceptible and -resistant strains): ≤1 mg/L; *Streptococcus pyogenes*, *S. agalactiae* and *S. dysgalactiae* subsp. *equisimilis*: ≤1 mg/L; and *E. faecalis* (vancomycin-susceptible): ≤4 mg/L. No breakpoints have been established by the NCCLS or FDA for other organisms.
b. No breakpoint has been established by the NCCLS or FDA.
c. Includes: *E. durans* (three strains), *E. gallinarum* (two strains) and *Enterococcus* non-speciated (six strains).

RESULTS

- Daptomycin was highly active against both *S. aureus* and coagulase-negative staphylococci (CoNS) (MIC_{50}, 0.25 mg/L and MIC_{90}, 0.5 mg/L for both) and was equally active against both oxacillin-resistant and oxacillin-susceptible subsets (**Table**).
- All *S. aureus* isolates were considered susceptible to daptomycin based on the susceptibility breakpoint (≤1 mg/L) recently approved by the FDA for this pathogen. In addition, all CoNS strains were inhibited by ≤1 mg/L of daptomycin.
- Daptomycin and linezolid were the most active compounds overall against enterococci with 100% of *E. faecalis* isolates susceptible (MIC_{90} 2 mg/L), and daptomycin activity was not affected by vancomycin resistance.
- Streptococcal isolates were susceptible to daptomycin with the highest MIC value being 1 mg/L. MIC_{90}s were 0.25 mg/L for both *S. pneumoniae* and β-haemolytic streptococci, and 0.5 mg/L for viridans group streptococci.
- Among *S. pneumoniae* isolates, 27.6% of strains were nonsusceptible to penicillin (MIC, ≥0.12 mg/L), but resistance to penicillin did not affect the activity of daptomycin (MIC_{90}, 0.25 mg/L).
- Among other Gram-positive organisms, *Corynebacterium* spp. (six isolates) were highly susceptible to daptomycin (MIC_{50}, ≤0.12 mg/L; range, ≤0.12 – 0.25 mg/L), while *Bacillus* spp. (two isolates) and *Listeria* spp. (five isolates) showed daptomycin MICs of ≥1 mg/L.

CONCLUSIONS

- The study demonstrated daptomycin to be highly active *in vitro* against a wide spectrum of Gram-positive pathogens isolated in European hospitals.
- Daptomycin activity against enterococci, staphylococci and streptococci was not affected by resistance to vancomycin, oxacillin or penicillin.
- The results of the present study coupled with the results of previous microbiologic, pharmacologic and clinical investigations indicate that this compound represents an excellent therapeutic option for complicated skin and soft tissue infections caused by Gram-positive cocci, especially multi-resistant strains.

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