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Antimicrobial Activity of Daptomycin (DAP) Tested Against 6737 Gram-positive (GP) Strains Collected From 3 Continents in 2002

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Abstract

Daptomycin (DAP) is a cyclic lipopeptide currently in phase 3 trials for the treatment of serious Gram-positive (GP) infections. We evaluated the *in vitro* activity of DAP against a contemporary worldwide collection of GP strains (2002). 6737 clinical GP strains were collected from more than 70 centers located in Europe, North America, and South America. The collection included *Staphylococcus aureus* (3202 strains, 39% oxacillin [OXA]-resistant [R]), coagulase-negative staphylococci ([CNS] 838 strains, 89% OXA-R), enterococci (819 strains, 10% vancomycin [VAN]-R), streptococci (1836 strains), and other GP species (42 strains). The strains were tested by NCCLS broth microdilution in Mueller-Hinton broth with 50 mg/L Ca^{2+} against DAP. More than 20 comparators were also tested by reference methods. DAP inhibited 99.4% of the strains at ≤2 µg/mL. The highest DAP MIC was 8 µg/mL (2 strains; 0.03%). The activity of DAP, VAN, teicoplanin (TEI), quinupristin-dalfopristin (Q-D) and linezolid (LZD) are shown in the table:

Activity of Antibiotics Tested

Organism (No. Tested)	$MIC_{50/90}$ (µg/mL) DAP	VAN	TEI	Q-D	LZD
S. aureus (3202)	0.25/0.5	1/1	0.5/1	0.25/0.5	2/2
CNS (838)	0.25/0.5	1/2	2/4	0.25/0.5	1/1
Streptococcus pneumoniae ([SPN] 1424)	≤0.12/0.25	0.25/0.5	≤0.12/2	0.25/0.5	1/1
β-hæmolytic streptococci (247)	≤0.12/0.25	0.25/1	≤0.12/≤0.12	0.25/0.5	1/1
Viridans group streptococci (149)	0.25/0.5	0.5/1	≤0.12/≤0.12	0.5/1	1/1
E. faecalis ([EF] 646)	1/1	1/4	≤0.12/0.25	8/>8	1/2
E. faecium ([EFM] 152)	2/4	1/>16	0.5/>16	1/2	2/2

DAP activity against other pathogens was ($MIC_{50/90}$ in µg/mL): *Corynebacterium* spp. (≤0.12/0.25), *Bacillus* spp. (1/2; 1 isolate at 8 µg/mL) and *Listeria* spp. (1/2). DAP was also very active against VAN-R EF (MIC_{90}, 1 µg/mL), VAN-R EFM (MIC_{90}, 4 µg/mL) and penicillin-resistant (PEN-R) *Streptococcus pneumoniae* (SPN) (MIC_{90}, 0.25 µg/mL). Among the 39 strains with DAP MIC results at 4 µg/mL, 87% were *E. faecium* (1 isolate at 8 µg/mL). VAN-resistant and Q-D-R in enterococci, PEN-R in SPN and OXA-R in staphylococci did not influence DAP activity. DAP showed a significant potency and spectrum against GP pathogens, including multi–drug-resistant (MDR) strains, and may represent a therapeutic option for infections caused by these pathogens following tests with appropriate media.

Introduction

Increasing resistance to antimicrobials has created a need to develop new antimicrobial agents. Daptomycin (DAP) is a novel cyclic lipopetide currently in phase 3 trials for the treatment of serious Gram-positive infections. DAP has a novel mechanism of action which targets the bacterial membrane. Thus, cross-resistance has not been observed with any other drug class.

DAP has rapid *in vitro* bactericidal activity against a wide spectrum of Gram-positive organisms, including multi–drug-resistant (MDR) strains of staphylococci, streptococci, and enterococci.

We evaluated the *in vitro* activity of DAP against a contemporary worldwide collection of Gram-positive strains isolated in 2002, including MDR strains.

Materials and Methods

Bacterial Isolates

6737 clinical Gram-positive strains were collected from more than 70 centers located in Europe, North America and South America in 2002. The collection included *Staphylococcus aureus* (3202 strains, 39% oxacillin-resistant [OXA-R]); coagulase-negative staphylococci (CNS) (838 strains, 89% OXA-R), enterococci (819 strains, 10% vancomycin-resistant [VAN-R]), streptococci (1836 strains) and other Gram-positive species (42 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 by NCCLS M7-A6 broth microdilution methods [NCCLS, 2003]. The test medium was Mueller-Hinton broth adjusted to contain physiologic levels of Ca^{2+} (50 mg/L) for testing DAP as recommended by NCCLS. A susceptible breakpoint of 2 µg/mL was used for comparison purposes only.

DAP was tested along with more than 20 comparator agents in microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio). Comparator agents included penicillin (PEN), OXA, VAN, teicoplanin (TEI), quinupristin-dalfopristin (Q-D), linezolid (LZD), levofloxacin (LEV), chloramphenicol (CHL), erythromycin (ERY), amoxicillin-clavulanate (A-C), tetracycline (TET), cliindamycin (CLI), doxycycline (DOX), ceftriaxone (CFT), and gentamicin (GEN). ATCC quality control organisms were performed concurrent with clinical isolate tests.

Results

- The overall distribution of DAP MICs ranged from ≤0.12-8 µg/mL (Table 1). Table 2 shows *in vitro* activity of 10 antimicrobial agents against all Gram-positive organisms worldwide. DAP inhibited 99.4% of all strains at ≤2 µg/mL.
- *Staphylococcus* spp. were 100.0% susceptible to DAP, VAN, and LZD. TEI and Q-D were >97.0% active against these *Staphylococcus* spp. isolates.
- DAP was equally active (100.0% susceptibility) against both OXA-R and -susceptible *Staphylococcus* spp. DAP $MICs_{50/90}$ were 0.25 and 0.5 µg/mL, respectively, for both *S. aureus* and coagulase-negative staphylococci.
- DAP showed low MIC values against *Streptococcus* spp. with the highest value being 1 µg/mL (15 strains). $MICs_{50/90}$ were ≤0.12 and 0.25 µg/mL, respectively, for both *Streptococcus pneumoniae* and β-hæmolytic streptococci, and 0.25 and 0.5 µg/mL for viridans-group streptococci.
- Among *S. pneumoniae*, 71.5% of strains were PEN-R, but resistance to PEN did not effect the activity of DAP (100.0% susceptibility). Only DAP and LZD were active against all *Streptococcus* spp. tested (100.0% susceptibility).
- Only 1 strain of *Enterococcus faecium* (0.1%) showed reduced susceptibility to DAP (MIC 8 µg/mL).
- *Enterococcus faecalis* isolates showed >96.0% susceptibility to DAP, PEN, VAN, TEI, and LZD. DAP exhibited higher activity against *E. faecalis* and *Enterococcus* spp. than against *E. faecium* strains. Among the 39 strains with DAP MIC results at 4 µg/mL, 87.0% were *E. faecium*.
- Decreased susceptibility to either VAN or Q-D did not effect the activity of DAP against enterococci.
- DAP activity ($MICs_{50/90}$ in µg/mL) against other pathogens was: *Corynebacterium* spp. (≤0.12/0.25), *Bacillus* spp. (1/2; 1 isolate at 8 µg/mL) and *Listeria* spp. (1/2).

Table 1. Analysis of DAP MIC Population Distributions for 12 Gram-positive Organism Species or Group (2002; 6737 isolates)

Organism (No. Tested)	Occurrences at MIC (µg/mL): ≤0.12	0.25	0.5	1	2	4	8[a]	16
S. aureus (3202)	139	2196	843	22	2	–	–	–
CNS (838)	120	508	187	21	2	–	–	–
E. faecalis (646)	1	28	254	313	47	3	–	–
E. faecium (152)	3	3	6	21	84	34	1	–
Enterococcus spp.[b] (21)	–	–	7	4	9	1	–	–
β-hæmolytic streptococci (247)	182	60	5	–	–	–	–	–
Viridans group streptococci (149)	57	45	37	10	–	–	–	–
S. pneumoniae (1424)	1044	352	23	5	–	–	–	–
S. bovis (16)	16	–	–	–	–	–	–	–
Bacillus spp. (10)	2	–	–	5	2	–	1	–
Corynebacterium spp. (14)	11	2	–	1	–	–	–	–
Listeria spp. (18)	–	1	–	6	10	1	–	–

[a]Proposed breakpoint for susceptibility (≤8µg/mL).
[b]Includes: *Enterococcus avium* (4 strains), *Enterococcus casseliflavus* (3 strains), *Enterococcus durans* (3 strains), *Enterococcus gallinarum* (4 strains), *E. raffinosus* (1 strain) and *Enterococcus* non-speciated (6 strains).

Table 2. Antimicrobial Activity of 10 Antimicrobial Agents Tested Against 6737 Strains of GP Bacteria Collected Worldwide in 2002

Organism/ Antimicrobial Agent (No. Tested)	MIC (µg/mL) 50%	90%	Range	% by Category Susceptible	Resistant
***S. aureus* (3202)**					
DAP[a]	0.25	0.5	≤0.12-2	100.0[b]	0.0[b]
PEN	16	>32	≤0.016->32	10.8	89.2
OXA	0.5	>8	≤0.06->8	61.1	38.9
VAN	1	1	0.25-2	100.0	0.0
CHL	8	16	≤2->16	89.7	3.4
TET	≤4	≤4	≤4->8	91.9	8.2
TEI	0.5	2	≤0.12-16	99.9	0.0
Q-D	0.25	0.5	≤0.06->8	99.8	0.1
LZD	2	2	≤0.25-16	100.0	0.0
LEV	0.25	>4	≤0.03->4	61.0	28.1
Coagulase-Negative staphylococci (838)					
DAP[a]	0.25	0.5	≤0.12-2	100.0[b]	0.0[b]
PEN	4	32	≤0.016->32	10.6	89.4
OXA	8	>8	≤0.06->8	20.2	79.8
VAN	1	2	≤0.12-4	100.0	0.0
CHL	4	8	≤2->16	91.2	8.6
TET	≤4	>8	≤2->8	85.4	14.6
TEI	2	4	≤0.12->16	97.6	0.5
Q-D	0.25	0.5	≤0.06->8	99.4	0.3
LZD	1	1	≤0.25-2	100.0	0.0
LEV	2	>4	≤0.03->4	50.3	34.0
***E. faecalis* (646)**					
DAP[a]	1	1	≤0.12-4	99.5[b]	0.0[b]
PEN	4	8	≤0.016->32	96.6	3.4
VAN	1	4	0.5->16	96.9	3.1
CHL	8	>16	≤2->16	80.3	18.4
DOX	>4	>4	≤0.5->4	43.2	56.8
TEI	≤0.12	0.5	≤0.12->16	97.8	2.2
Q-D	8	>8	≤0.25->8	0.6	88.7
LZD	1	2	≤0.25-4	99.8	0.0
LEV	>4	>4	0.25->4	57.9	41.5
GEN (high-level)	≤500	>1000	≤500->1000	–	34.4
***E. faecium* (152)**					
DAP[a]	2	4	≤0.12-8	100.0[b]	0.0[b]
PEN	>32	>32	0.5->32	15.8	84.2
VAN	1	>16	0.25->16	63.8	34.2
CHL	8	16	≥2->16	88.8	4.6
DOX	≤0.5	>4	≤0.5->4	65.3	34.7
TEI	0.5	>16	≤0.12->16	69.1	25.0
Q-D	1	2	0.25-8	73.0	6.5
LZD	2	2	≤0.25->16	99.3	0.7
LEV	>4	>4	0.25->4	21.7	74.3
GEN (high-level)	≥500	>1000	≤500->1000	–	29.8
***Enterococcus* spp.[c] (21)**					
DAP	1	2	0.5-4	100.0[b]	0.0[b]
PEN	4	>32	0.5->32	100.0	0.0
VAN	1	8	0.5->16	85.7	4.8
CHL	4	>16	4->16	76.2	9.5
DOX	2	>4	≤0.5->4	57.1	42.9
TEI	0.5	2	≤0.12->16	95.2	4.8
Q-D	1	4	0.5-4	52.3	23.8
LZD	2	2	0.5-2	100.0	0.0
LEV	2	>4	0.25->4	76.2	14.3
GEN (high-level)	≤500	>1000	≤500->1000	–	29.8
β-hæmolytic streptococci (247)					
DAP[a]	≤0.12	0.25	≤0.12-0.5	100.0[b]	0.0[b]
PEN	≤0.016	0.06	≤0.016-0.12	100.0	0.0
A-C	≤2	≤2	≤2	–[b]	–[b]
CFT	≤0.25	≤0.25	≤0.25	100.0	0.0
VAN	0.25	1	≤0.12-1	100.0	0.0
CLI	≤0.06	≤0.06	≤0.06->8	94.3	5.7
ERY	≤0.06	2	≤0.06->8	82.1	17.0
Q-D	0.25	0.5	≤0.06-1	100.0	0.0
LZD	1	1	≤0.25-2	100.0	0.0
LEV	0.5	1	0.06->4	98.0	1.2

Organism/ Antimicrobial Agent (No. Tested)	MIC (µg/mL) 50%	90%	Range	% by Category Susceptible	Resistant
Viridans group streptococci (149)					
DAP[a]	0.25	0.5	≤0.12-1	100.0	0.0[b]
PEN	0.06	1	≤0.016-8	79.2	3.4
A-C	≤2	≤2	≤2-16	–[b]	–[b]
CFT	≤0.25	0.5	≤0.25-8	95.3	1.4
VAN	0.5	1	≤0.12-1	100.0	0.0
CLI	≤0.06	8	≤0.06->8	85.8	11.5
ERY	≤0.06	>8	≤0.06->8	61.1	32.2
Q-D	0.5	1	≤0.06-2	99.3	0.0
LZD	1	1	≤0.06-2	100.0	0.0
LEV	1	2	≤0.03->4	95.3	4.7
***S. pneumoniae* (1424)**					
DAP	≤0.12	0.25	≤0.12-1	100.0[b]	0.0[b]
PEN	≤0.03	2	≤0.03-8	71.5	14.3
A-C	≤0.06	2	≤0.06-16	97.0	1.7
CFT	0.03	1	≤0.008-8	98.4	0.7
VAN	0.25	0.5	≤0.06-2	100.0	–[b]
CLI	≤0.06	>8	≤0.06->8	86.8	12.6
ERY	≤0.25	>32	≤0.25->32	73.4	25.0
Q-D	0.25	0.5	≤0.06-1	100.0	0.0
LZD	1	1	≤0.25-2	100.0	0.0
LEV	1	1	≤0.03->4	98.7	1.3
***S. bovis* (16)**					
DAP[a]	≤0.12	≤0.12	≤0.12	100.0[b]	0.0[b]
PEN	0.06	0.12	0.03-0.12	100.0	0.0
VAN	0.25	0.5	0.25-0.5	100.0	0.0
CHL	≤2	≤2	≤2-4	100.0	0.0
DOX	>4	>4	≤0.5->4	–	–
TEI	≤0.12	≤0.12	≤0.12-0.25	100.0	0.0
Q-D	0.25	1	0.12-1	100.0	0.0
LZD	1	1	0.5-1	100.0	0.0
LEV	1	1	0.5-1	100.0	0.0
***Bacillus* spp.[d] (10)**					
DAP	1	2	≤0.12-8	100.0[b]	0.0[b]
PEN	32	>32	≤0.12->32	10.0	90.0
A-C	8	16	≤2->12	40.0	60.0
CFT	32	>32	16->32	0.0	50.0
VAN	1	1	1	100.0	0.0
CHL	4	4	≤2->4	100.0	0.0
TEI	≤0.12	>2	≤0.12->2	100.0	0.0
Q-D	1	1	0.25-1	100.0	0.0
LZD	1	1	0.5-1	100.0	0.0
LEV	0.12	0.12	0.06-0.25	100.0	0.0
***Corynebacterium* spp.[d] (14)**					
DAP	≤0.12	0.25	≤0.12-1	100.0[b]	0.0[b]
PEN	4	>32	≤0.016->32	14.3	85.7
A-C	4	>16	≤2->16	57.1	42.9
CFT	16	>32	≤0.25->32	42.9	21.4
VAN	0.25	1	≤0.12-1	100.0	0.0
CHL	≤2	8	≤2->16	92.9	0.0
TEI	0.25	>2	≤0.12-4	100.0	0.0
Q-D	0.25	0.5	≤0.25-0.5	100.0	0.0
LZD	≤0.25	1	≤0.25-1	100.0	0.0
LEV	4	>4	0.12->4	35.7	21.4
***Listeria* spp. (18)**					
DAP[a]	1	2	0.25-4	94.4[b]	0.0[b]
PEN	0.5	0.5	0.25-2	–	–
VAN	1	1	0.25-1	–	–
CHL	4	8	4-16	–	–
DOX	≤0.5	≤0.5	≤0.5	–	–
TEI	≤0.12	≤0.12	≤0.12-0.25	–	–

[a]A susceptible breakpoint of 8 µg/mL (resistant at ≥8 µg/mL) was used for comparison purposes only.
[b]No breakpoint has been established by the NCCLS (2003).
[c]Includes: *E. avium* (4 strains), *E. casseliflavus* (3 strains), *E. durans* (3 strains), *E. gallinarium* (4 strains), *E. raffinosus* (1 strain) and *Enterococcus* non-speciated (6 strains).
[d]Staphylococcal breakpoints were used for comparison purposes only.

Conclusions

- DAP was very active against MDR GP pathogens, including:
  - VAN-R enterococci
  - Q-D-R enterococci and staphylococci
  - OXA-R staphylococci
  - PEN-R streptococci
- DAP exhibited excellent *in vitro* activity against a wide spectrum of GP pathogens and could represent an excellent therapeutic option for infections caused by MDR GP pathogens

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