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In Vitro Activities of Quinupristin/Dalfopristin and Eight Other Antimicrobial Agents against 360 Clinical Isolates from Korea

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Abstract

The emergence of multi-drug resistant gram-positive cocci such as methicillin-resistant (MR) staphylococci, vancomycin-resistant (VR) enterococci, and vancomycin-intermediate resistant *S. aureus* (VISA) has given new urgency to the development of new antimicrobial agents. One of these is quinupristin/dalfopristin (Q/D). We decided to determine the susceptibility of gram-positive cocci isolated at two university hospitals in Seoul to Q/D and compare the results with eight other antimicrobial agents. We investigated 120 isolates of *S. aureus* including 49 MRSAs and one VISA, 120 isolates of coagulase negative staphylococci (CNS), 64 *E. faecalis* and 56 *E. faecium*, including seven strains of VR *E. faecium*. Minimum inhibitory concentrations (MICs) and minimal bactericidal concentrations (MBCs) for several antimicrobials, including vancomycin and Q/D, were determined by broth microdilution. All *S. aureus* including VISA were susceptible to Q/D. Q/D MIC_{90} for both methicillin-susceptible *S. aureus* (MSSA) and MRSA was 0.25 g/mL. 49 (87.5%) of 56 *E. faecium* including six of seven VR *E. faecium* were susceptible to Q/D. *E. faecalis* were not susceptible to Q/D (only 1.5% susceptible), but were inhibited by ampicillin (94% susceptible) or vancomycin (95%). CNS was susceptible to Q/D (96% susceptible) and vancomycin (100% susceptible). One of 38 staphylococci and two of 17 *E. faecium* were tolerant to Q/D. In conclusion, Q/D showed excellent activity against all species of gram-positive cocci including MRSA, VISA, and VR *E. faecium* except *E. faecalis*, and may provide a valuable option for the treatment of infections caused by these emerging nosocomial pathogens of gram-positive cocci.

Key Words: Quinupristin/dalfopristin (Q/D), multi-drug resistant, MRSA, enterococci

INTRODUCTION

The emergence of antimicrobial resistance, particularly among the gram-positive pathogens, has been rapid and alarming. Vancomycin and teicoplanin have been considered as the drugs of "last resort" for the treatment of serious infections due to drug-resistant gram-positive pathogens, because of their outstanding activities against a wide variety of gram-positive bacteria. However, vancomycin-resistant enterococci (VRE) began to be recognized in the late 1980s in the U.K.,[1] and this was quickly followed in the U.S.A.[2] VRE were detected for the first time in 1992 in Korea[3] and the incidence of VRE among clinical isolates has greatly increased to 7.7 % in 1996.[4] More recently, there have been several reports of intermediate-level resistance to vancomycin and teicoplanin in clinical isolates of both coagulase-negative staphylococci (CNS) and *Staphylococcus aureus* in Japan,[5] U.S.A.[6,7] and Korea[8] (vancomycin-intermediate resistant *S. aureus*, or VISA).

The emergence of multi-drug resistant gram-positive pathogens has given new urgency to the development of antimicrobial agents with efficacy against these organisms. One of these is quinupristin/dalfopristin (Q/D),[9] which is a water-soluble synthetic streptogramin, a combination of quinupristin and dalfopristin at a ratio of 30 : 70.[9] Q/D binds irreversibly to bacterial ribosomes, thereby inhibiting protein synthesis.[10] Early in vitro studies suggested that Q/D had good activity against *Staphylococcus* species, including methicillin-resistant strains, *Streptococcus* species, including penicillin-resistant strains, and selected *Enterococcus* species, including glycopeptide-resistant strains,

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except *Enterococcus faecalis*.[11,12]

The purpose of this study was to determine and compare the antimicrobial activity of Q/D with other antimicrobial agents against *S. aureus*, CNS, *E. faecium*, and *E. faecalis*, recently isolated from clinical specimens at two tertiary care hospitals in Seoul, Korea.

MATERIALS AND METHODS

Bacterial strains

Two tertiary-care hospitals in Seoul were recruited into the study; the following gram-positive bacterial species were tested: -1) Methicillin-susceptible and -resistant *S. aureus* (120 strains), including a VISA strain (vancomycin MIC, 8 μg/mL; teicoplanin MIC, 16 μg/mL); 2) Methicillin-susceptible and -resistant CNS (120 strains); 3) *E. faecalis* (64 strains); and 4) *E. faecium* (56 strains).

All strains were isolated from clinical specimens. Only one isolate from a patient was tested. All strains were identified to the species level except CNS.

Species identification

The isolates from blood, body fluid (or abscess), and cerebrospinal fluid were identified by the MicroScan PosCombo type 6 (Dade-Behring Inc., West Sacramento, CA, USA). The other specimens were identified by latex agglutination for *S. aureus* (PS latex; Eiken Co., Tokyo, Japan) and conventional biochemical tests. CNS strains with resistance to Q/D were identified with the MicroScan PosCombo type 12. *E. faecium* strains with resistance to Q/D were identified by supplementary tests, such as arabinose fermentation, tellurite tolerance and ampicillin susceptibility.[13]

Antimicrobial agents

The study drugs against *S. aureus* and CNS were Q/D (Rhone-Poulenc Rorer, Collegeville, Pennsylvania, USA), oxacillin, vancomycin, erythromycin, clindamycin, and ciprofloxacin (Bayer AG, Leverkusen, Germany), gentamicin, rifampin, and teicoplanin (Hoechst-Marion-Roussel, Bridgewater, NJ, USA). The study drugs against *E. faecium* and *E. faecalis* were Q/D, vancomycin, erythromycin, tetracycline, chloramphenicol, ampicillin, ciprofloxacin, rifampin, and teicoplanin. All antimicrobials, manufacturers unspecified, were purchased from the Sigma Chemical Company (St. Louis, MO, USA).

In vitro susceptibility test

Minimum inhibitory concentration (MIC): MICs of antimicrobial agents were determined by the microdilution method according to the National Committee for Clinical Laboratory Standards (NCCLS) guidelines.[14] Reference strains of *S. aureus* ATCC 29213, and *E. faecalis* ATCC 29212 were used for quality control.[15] The following NCCLS-approved susceptibility breakpoints were used for Q/D: susceptible, ≤ 1 μg/mL; intermediate, 2 μg/mL; and resistant, ≥ 4 μg/mL.[16]

Minimum bactericidal concentration (MBC): MBC was determined by performing quantitative subcultures on each well showing no visible growth on MIC determination. When the ratio of MBC to MIC was 32 or greater, for a given bacterium-antimicrobial agent combination, the organism was said to be tolerant to the action of the antimicrobial agent.[17] For MBC determination, 20 strains each of *S. aureus*, CNS and *E. faecium* and 15 strains of *E. faecalis* were randomly selected from strains that were susceptible to as many antimicrobial agents as possible, including Q/D.

Statistics

The Chi Square test was used to compare the antimicrobial susceptibilities of MSSA and MRSA, using MedCalc software, version 4.20 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Activity of Q/D against staphylococci

The results of susceptibility testing upon 120 strains of *S. aureus* are summarized in Table 1. Q/D was the only one of the 9 antimicrobials tested, which was active against all strains of staphylococci including both MSSA and MRSA. All with the exception of one strain were susceptible to vancomycin and

Table 1. Activities of Q/D and 8 Other Antimicrobial Agents against *S. aureus*

Antimicrobial agents	Methicillin-susceptible (n=71)				Methicillin-resistant (n=49)			
	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC range (μg/mL)	% Susceptible	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC range (μg/mL)	% Susceptible
Q/D	0.25	0.25	0.06−0.5	100.0	0.25	0.25	0.06−1.0	100.0
Vancomycin	1.0	1.0	0.125−2	100.0	1.0	2	0.5−4	98.0
Teicoplanin	0.5	1.0	0.03−2	100.0	2	8	0.125−16	98.0
Clindamycin	0.125	0.25	0.06−>128	95.8	>128	>128	0.06−>128	32.7
Ciprofloxacin	0.5	2.0	0.125−32	85.9	32	>128	0.125−>128	32.7
Rifampin	0.008	0.015	0.002−0.5	100.0	0.008	4	0.003−128	87.8
Erythromycin	0.5	>128	0.125−>128	60.6	>128	>128	0.5−>128	4.1
Gentamicin	1.0	128	0.06−>128	66.2	64	>128	0.5−>128	8.2
Oxacillin	0.5	1.0	0.125−2	100.0	>128	>128	8−>128	0.0

Table 2. Activities of Q/D and 8 Other Antimicrobial Agents against CNS

Antimicrobial agents	Methicillin-susceptible (n=15)				Methicillin-resistant (n=105)			
	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC range (μg/mL)	% Susceptible	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC range (μg/mL)	% Susceptible
Q/D	0.125	0.125	0.06−1.0	93.3	0.25	0.5	0.06−64	96.2
Vancomycin	1.0	2	0.25−2	100.0	2	2	0.5−4	100.0
Teicoplanin	0.5	4	<0.125−8	100.0	4	8	0.125−16	99.0
Clindamycin	<0.125	0.25	<0.125−0.25	100.0	>128	>128	<0.125−<128	32.4
Ciprofloxacin	<0.125	0.25	<0.125−0.5	100.0	8	128	0.08−128	44.8
Rifampin	0.002	0.015	0.002−0.125	100.0	4	>128	0.002−>128	48.6
Erythromycin	0.25	128	<0.125−128	73.3	>128	>128	<0.125−>128	17.1
Gentamicin	0.25	8	<0.125−16	86.7	64	>128	0.06−>128	13.3
Oxacillin	<0.125	0.25	<0.125−0.25	100.0	64	>128	0.5−>128	0.0

teicoplanin. While the MIC_{90} of vancomycin and teicoplanin for MRSA were 2- to 8- fold higher than those for MSSA, Q/D was equally active against MSSA and MRSA (MIC_{90} values both 0.25 μg/mL). One result of note was that a VISA strain was found susceptible to Q/D (MIC=0.5 μg/mL). Compared with MSSA, MRSA were much less susceptible to other antimicrobials including clindamycin, ciprofloxacin, erythromycin, and gentamicin ($p<0.01$). Erythromycin and gentamicin were rarely active against MRSA.

The activities of Q/D and other antimicrobials against CNS were similar to those found against *S. aureus*, except that one strain of MSCNS and four strains of MRCNS were not susceptible to Q/D. *S. sciuri* (one strain) and *S. epidermidis* (three strains) were identified as Q/D-resistant MRCNS strains. A single remaining Q/D-resistant MSCNS strain could not be identified due to problems of specimen storage. With the exception of vancomycin and teicoplanin, the other antimicrobials were less active against MRCNS than MSCNS ($p<0.01$, Table 2).

No strains of *S. aureus* were tolerant to vancomycin, teicoplanin, ciprofloxacin, or oxacillin. One of 20 strains was tolerant to Q/D and 10 of the 19 strains to rifampin (Table 3). CNS strains were not tolerant to any of the antimicrobial agents except rifampin (one strain), clindamycin (two strains), and erythromycin (two strains).

Activity of Q/D against enterococci

Q/D was active against *E. faecium* with an MIC_{50} and an MIC_{90} of 0.5 and 2.0 μg/mL, respectively (Table 4). Only one of the 56 *E. faecium* isolates was found to be resistant to Q/D. Initially eight isolates

Table 3. Tolerance of Staphylococci*

Antimicrobial agents	*S. aureus*		CNS	
	No. tolerant/ No. tested (%)	Median MBC/MIC ratio (range)	No. tolerant/ No. tested (%)	Median MBC/MIC ratio (range)
Q/D	1/20 (5.0)	3.0 (1−32)	0/18 (0.0)	2 (1−16.7)
Vancomycin	0/20 (0.0)	2 (1−16)	0/20 (0.0)	1 (1−2)
Teicoplanin	0/20 (0.0)	1 (1−8.3)	0/20 (0.0)	2 (0.5−4)
Clindamycin	6/16 (37.5)	8 (4−64)	2/12 (16.7)	3 (1−64)
Ciprofloxacin	0/19 (0.0)	1 (1−8)	0/13 (0.0)	2 (1−8)
Rifampin	10/19 (52.6)	35.7 (0.5−83.3)	1/15 (0.7)	2 (1−35.7)
Erythromycin	0/15 (0.0)	4 (1−16)	2/12 (16.7)	3 (1−64)
Gentamicin	0/19 (0.0)	2 (1−4)	0/16 (0.0)	2 (1−8)
Oxacillin	0/18 (0.0)	1.5 (1−16)	0/15 (0.0)	2 (1−8)

*A strain was considered tolerant when the MBC/MIC ratio was 32.

Table 4. Activities of Q/D and 8 Other Antimicrobial Agents against Enterococci

Antimicrobial agents	*E. faecalis* (n=64)				*E. faecium* (n=56)			
	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC range (μg/mL)	% Susceptible	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	MIC range (μg/mL)	% Susceptible
Q/D	8	16	0.25−32	1.5	0.5	2	0.06−4	87.5
Vancomycin	2	4	0.25−>128	95.3	1	>128	0.25−>128	87.5
Teicoplanin	0.25	0.5	0.25−>128	96.9	0.5	32	<0.125−>128	89.3
Ampicillin	1	4	0.25−128	93.8	64	>128	0.25−>128	32.1
Chloramphenicol	8	64	2−64	50.0	8	64	2−64	58.9
Ciprofloxacin	2	128	0.25−>128	40.6	4	>128	0.5−>128	25.0
Erythromycin	>128	>128	0.25−>128	7.8	>128	>128	<0.125−>128	5.4
Rifampin	4	32	0.25−>128	25.0	16	32	0.025−>128	16.1
Tetracycline	64	64	0.125−>128	20.3	16	64	0.125−128	39.3

Table 5. Activities of Q/D and 8 Other Antimicrobial Agents against Vancomycin-resistant *E. faecium*

Antimicrobial agents	Strain, MIC (μg/mL)						
	E43	E47	E53	E54	E55	E56	E60
Q/D	0.5	2.0	0.5	1.0	0.5	0.5	0.5
Vancomycin	>128	>128	>128	>128	>128	>128	>128
Teicoplanin	128	32	64	32	128	8	32
Ampicillin	128	32	>128	32	64	32	128
Rifampin	>128	16	16	16	16	4	4
Chloramphenicol	8	16	8	16	16	8	8
Ciprofloxacin	32	8	64	>128	>128	4	8
Erythromycin	>128	>128	>128	>128	>128	>128	>128
Tetracycline	16	64	32	32	0.5	0.25	0.25

Table 6. The Tolerance of Enterococci

Antimicrobial agents	*E. faecalis*		*E. faecium*	
	No. tolerant/ No. tested (%)	Median MBC/MIC ratio (range)	No. tolerant/ No. tested (%)	Median MBC/MIC ratio (range)
Q/D	0/11 (0.0)	2 (1−8)	2/17 (11.8)	2 (1−64)
Vancomycin	4/15 (26.7)	2 (1−128)	5/17 (29.4)	2 (1−128)
Teicoplanin	2/12 (16.7)	4 (2−32)	5/18 (27.8)	8 (2−64)
Ampicillin	5/11 (45.4)	16 (8−64)	1/12 (8.3)	16 (1−32)
Chloramphenicol	0/10 (0.0)	3 (1−16)	0/11 (0.0)	4 (2−16)
Ciprofloxacin	0/9 (0.0)	1 (1−8)	0/15 (0.0)	2 (1−4)
Erythromycin	3/5 (60.0)	32 (4−64)	1/7 (14.3)	2 (1−32)
Rifampin	0/11 (0.0)	1 (0.2−4)	1/14 (7.1)	3 (1−66.7)
Tetracycline	2/8 (37.5)	8 (2−64)	3/19 (15.8)	2 (1−64)

were thought to be resistant, but seven of those were confirmed as *E. faecalis* by supplementary tests. Six of seven vancomycin-resistant strains of *E. faecium* were also susceptible to Q/D (Table 5). The only other antimicrobial that showed considerable activity against vancomycin-resistant *E. faecium* was chloramphenicol; four of the seven vancomycin-resistant *E. faecium* were susceptible. Only two of 17 strains of *E. faecium* were tolerant to Q/D and these two were resistant to erythromycin (Table 6).

Almost all *E. faecalis* isolates were resistant to Q/D (MIC_{50}, 8 μg/mL) and erythromycin (MIC_{50}, >128 μg/mL). Ampicillin was active against 93.8% of *E. faecalis*, as were vancomycin and teicoplanin, 95.3% and 96.9% of strains, respectively (Table 4).

There were no enterococcal strains tolerant to chloramphenicol and ciprofloxacin (Table 6), while nine of the 32 enterococci strains were tolerant to vancomycin and seven of the 30 strains were tolerant to teicoplanin, only two of 28 strains were tolerant to Q/D (Table 6).

DISCUSSION

This study showed that Q/D was the most active antimicrobial agent among the 9 drugs tested against *S. aureus* (100.0% susceptible), CNS (93.3% susceptible), and *E. faecium* (87.5% susceptible). Our results were similar to those of the multicenter study,[11] in which the susceptibility of *S. aureus*, CNS, and *E. faecium* to Q/D were 99.9%, 100.0%, and 92.0%, respectively. Q/D was equally active against MSSA and MRSA, while MRSA had increased MIC to vancomycin, teicoplanin, and more resistance to clindamycin, ciprofloxacin, rifampin, erythromycin, and gentamicin than MSSA. Q/D was also active against a single VISA strain.

Q/D and related antibiotics (the lincosamides and macrolides) are inhibitors of bacterial protein synthesis and the cross-resistance between erythromycin and quinupristin is well known.[18] Mouton et al.[19] showed that there is a significant correlation between the sensitivity to erythromycin and Q/D for viridans streptococci. In addition, several studies reported that the bactericidal effects of Q/D on *E. faecium* are influenced by its resistance to erythromycin.[20,21] However, for *S. aureus* and CNS in this study, there was no significant difference in susceptibility to Q/D between the erythromycin-resistant and erythromycin-susceptible strains.

In this study, only one of the 56 *E. faecium* isolates was found to be resistant to Q/D. Initially, eight isolates were thought to be resistant, but verification of species identification showed that seven of the eight isolates had been erroneously identified as *E. faecium*, they were in fact *E. faecalis*. Jones et al.[11] reported that 94.7% of *E. faecium* strains showing resistance to Q/D were re-identified as *E. faecalis* and that in fact 0.2% of *E. faecium* isolates were truly resistant to Q/D. Thus, clinical microbiology laboratories should check for the possibility of this misidentification, if an *E. faecium* strain is found to be resistant to Q/D. Supplementary tests such as arabinose fermentation, tellurite tolerance and the examination of antimicrobial susceptibility patterns

could minimized the incidences of these erroneous results.

E. faecalis was found to be refractory to Q/D as reported previously,[22,23] but reserved susceptibility to vancomycin, teicoplanin, and ampicillin. Q/D was one of the most active drugs to *E. faecium*. The MIC_{90} of Q/D for *E. faecium* ranged from 0.5 to 2 μg/mL, and seven vancomycin-resistant *E. faecium* strains were susceptible to Q/D. Because Q/D has also been approved by the FDA for the treatment of vancomycin-resistant *E. faecium* infection,[24] it would be the first choice for vancomycin-resistant *E. faecium* infection in future.

This study also demonstrated that Q/D had good bactericidal activities in vitro against gram-positive bacteria including *S. aureus*, CNS, and *E. faecium*, which show no significant tolerance. Boswell et al.[25] have reported that raised MBCs to Q/D, which is at least four-fold higher than the MIC are associated with tolerance in *S. aureus*. Boswell et al.[26] evaluated the time-kill kinetics of 2 mg/L Q/D on *S. aureus* strains with raised and normal MBCs to Q/D". Initially the killing activities against strains with raised and normal MBCs were very similar. However, the reduction in viability at 24 h was significantly higher for *S. aureus* with the normal MBC. Since tolerance is known to be an important factor for predicting the failure of antimicrobial therapy in patients with staphylococcal endocarditis,[27] Q/D may be useful for the treatment of endocarditis due to staphylococci or other gram positive cocci.

In conclusion, Q/D was active against staphylococci and enterococci except *E. faecalis*. Furthermore, no significant level of tolerance was shown to Q/D by these organisms. Of particular significance is the finding that Q/D showed excellent activities against MRSA including VISA, and vancomycin-resistant *E. faecium*, which suggests that Q/D may provide a valuable option for the treatment of infections caused by these emerging gram-positive pathogens, especially, MRSA, VRE, and VISA.

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