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Postantibiotic Effect and Postantibiotic Sub-MIC Effect of Quinupristin-Dalfopristin against Gram-Positive and -Negative Organisms

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Quinupristin-dalfopristin produced postantibiotic effects (PAEs) and postantibiotic sub-MIC effects of >2 h against 18 gram-positive cocci. Mean pneumococcal and staphylococcal PAEs were 2.8 and 4.7 h, respectively, with shorter PAEs for constitutively than inducibly macrolide-resistant staphylococci. Mean PAEs for vancomycin-susceptible and -resistant *Enterococcus faecium* were 8.5 and 2.6 h, respectively.

The rate of bacterial killing, postantibiotic effect (PAE), and effects of sub-MICs are important pharmacodynamic parameters that can provide the theoretical basis for design of antimicrobial dosing regimens (7, 15). Quinupristin-dalfopristin (RP 59500; Synercid) is a recently developed combination of two streptogramins (A and B) designed for parenteral administration. Previous studies have documented in vitro killing of pneumococci by this compound (4). Quinupristin-dalfopristin is also rapidly bactericidal against *Streptococcus pneumoniae*, reducing bacterial counts by 90% after as little as 1 h of exposure (14). The compound may be bactericidal but is most often bacteriostatic against *Enterococcus faecium* but not active against *E. faecalis* (6, 16).

Quinupristin-dalfopristin produces long PAEs with gram-positive organisms. It has also been shown to produce PAEs of 2 to 8 h against *Staphylococcus aureus*, 7.5 to >9 h against *S. pneumoniae*, and >18 h against *Streptococcus pyogenes* (3, 5, 11). In one study, shorter PAEs were reported for constitutively macrolide-resistant staphylococci than for inducible strains (5). In another study, shorter PAEs were reported for methicillin-resistant *S. aureus* strains than for susceptible strains (11).

The postantibiotic sub-MIC effect (PA-SME) and sub-MIC effect (SME) are pharmacodynamic parameters related to the PAE (12, 13). Our purpose was to study the PAEs and PA-SMEs of quinupristin-dalfopristin against 18 gram-positive cocci, including pneumococci, staphylococci, and *E. faecium* (see Tables 1 to 3).

The organisms used were recent clinical isolates from Hershey Medical Center and included one methicillin-susceptible, erythromycin-susceptible *S. aureus* strain, two methicillin-resistant, erythromycin-susceptible *S. aureus* strains, two methicillin-resistant, inducibly macrolide-resistant and two methicillin-resistant, constitutively macrolide-resistant *S. aureus* strains, two methicillin-susceptible and two methicillin-resistant, coagulase-negative staphylococcal strains, one penicillin-susceptible, one intermediately penicillin-resistant, and one penicillin-resistant pneumococcal strain, and two vancomycin-susceptible and two vancomycin-resistant *E. faecium* strains.

Standard broth microdilution using Mueller-Hinton broth (MHB) with added lysed horse blood for pneumococci was used (10). *S. aureus* strains were defined as constitutively or inducibly macrolide resistant by the double-disk method (9).

PAE (7) was determined by the viable plate count method using MHB (Difco) supplemented with 5% lysed horse blood for testing of pneumococci.

The PAE was induced by exposure to 10 times the MIC of RP 59500 for 1 h, except in experiments with pneumococci. Because RP 59500 is rapidly bactericidal against pneumococci, it was tested at the MIC, 0.5 times the MIC, and 0.25 times the MIC. For vancomycin-susceptible *E. faecium* strains, although they are susceptible at the MIC, 10 times the MIC is not clinically achievable, and exposures were at 10 and 0.25 times the MIC, respectively.

For PAEs, tubes containing 5 ml of MHB with antibiotic were inoculated with approximately 5×10^6 CFU of the test bacteria per ml (range, 10^6 to 10^7 CFU/ml) (13). Growth controls with inoculum but no antibiotic were included with each experiment. Inoculated test tubes were placed in a shaking water bath at 35°C for an exposure period of 1 h. At the end of the exposure, cultures were diluted 1:1,000 in prewarmed broth to remove the antibiotic.

Viability counts were determined before exposure, immediately after dilution (0 h), and then every 2 h until the turbidity of the tube reached a no. 1 McFarland standard. Viability counts were performed as described previously (13). The PAE was defined as described by Craig and Gudmundsson (7).

The PA-SME and SME (13) were measured in three experiments. Separate cultures for determining PA-SME and SME were prepared, and each was inoculated with approximately 5×10^6 CFU/ml (13). In cultures designated for PA-SME determination, the PAE was induced as described above. Following 1:1,000 dilution in MHB to remove the antibiotic, cultures were divided among five tubes. To four of these tubes, RP 59500 was added to make final sub-MICs of 0.1, 0.2, 0.3, and 0.4 times the MIC, respectively. The remaining tube did not receive an antibiotic and served as a growth control. Tubes were incubated in a shaking water bath at 35°C. Viability counts were determined before exposure, immediately after dilution, and then every 2 h until the turbidity reached a no. 1 McFarland standard. The PAE was not induced in cultures designated for SME testing. In all other respects, SME cultures were treated as described above for PA-SME determination. PA-SMEs and SMEs were defined as described by Odenholt-Tornqvist (12).

For each PAE, SME, or PA-SME experiment, viability

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counts, expressed as $\log_{10}$ CFU per milliliter, were plotted against time. Results were expressed as the mean and range of three separate assays.

The quinupristin-dalfopristin MIC for pneumococci was 0.5 μg/ml. The MICs were 0.125 to 0.5 μg/ml for all of the groups of staphylococci tested. Erythromycin MICs for susceptible staphylococci were ≤0.25 and >64.0 μg/ml for inducibly and constitutively macrolide-resistant strains. The quinupristin-dalfopristin MIC was 2.0 μg/ml for vancomycin-susceptible *E. faecium* and 0.5 μg/ml for vancomycin-resistant (>64.0 μg/ml) *E. faecium*.

When the three pneumococcal strains were exposed to quinupristin-dalfopristin at 0.5 times the MIC for 1 h, the mean PAE was 2.8 h (range, 1.7 to 4.1 h). Pneumococcal PA-SMEs were generally longer than the sum of the PAE and the SME (Table 1). This indicates that sub-MICs delayed the regrowth of strains when they had been pre-exposed to suprainhibitory levels.

The mean PAE for all staphylococci was 4.7 h. For two methicillin-resistant *S. aureus* strains constitutively resistant to macrolides, the PAEs and PA-SMEs were shorter than those for the two inducibly resistant strains. The mean PAE for constitutively resistant *S. aureus* was 2.4 h, compared to 5.6 h for inducibly resistant strains (Table 2).

PAEs and PA-SMEs were shorter for vancomycin-resistant than for susceptible *E. faecium*. The mean PAE for vancomycin-resistant strains was 2.6 h, compared to 8.5 h for vancomycin-susceptible strains exposed to 10 and 0.25 times the MIC (Table 3).

Quinupristin-dalfopristin MICs were similar to those described previously (5). In this study, quinupristin-dalfopristin produced long (>2 h) PAEs against all of the strains tested. A previous study with healthy human volunteers has shown that 7.0- to 12.6-mg/kg doses administered as a 1-h infusion achieved peak drug concentrations in serum of approximately 5.0 to 11.0 mg/kg, respectively. The serum elimination half-life is 1.0 to 1.5 h (8). For measurement of PAE and PA-SME, all of the strains used in this study were exposed to quinupristin-dalfopristin below clinically achievable levels.

Our results confirm previous reports that, compared to other staphylococci, for constitutively erythromycin-resistant, methicillin-resistant *S. aureus* strains the PAEs are shorter than those for inducible strains (5). Our results also indicate that for vancomycin-resistant strains of *E. faecium*, the PAEs are considerably shorter than those for vancomycin-susceptible strains. These results may reflect the fact that a strain still susceptible to the combination of streptogramins A and B is not killed when the strain carries a streptogramin A resistance determinant (*vatA*, *vatB*, *vgA*, or *satA*) (1).

In general, we found that PA-SMEs exceeded both PAEs and SMEs for all of the strains tested. Because the PA-SME exceeded the sum of the PAE and the SME, sub-MICs of quinupristin-dalfopristin had a greater effect on pre-exposed cultures (PAE phase) than on unexposed cultures (11). This suggests that a very long period of growth inhibition can be achieved by sub-MICs of quinupristin-dalfopristin when they follow a suprainhibitory level in vivo. This is clinically important because sub-MICs may persist between doses when an intermittent dosing regimen is used.

The relatively short serum elimination half-life of quinupristin-dalfopristin would normally require dosing every 4 to 7 h. However, the prolonged PAEs and PA-SMEs found in this study would allow more widely spaced dosing intervals without loss of efficacy. Also, the active metabolites of both streptogramin components (2) should have an important effect on the dosing. Therefore, the prolonged PAEs and PA-SMEs found

TABLE 1. PAEs, SMEs, and PA-SMEs of quinupristin-dalfopristin for pneumococci

Strain (penicillin susceptibility)[a]	Exposure concn (× MIC)[b]	Mean (range) effect (h)[c]							
		0.1 × MIC		0.2 × MIC		0.3 × MIC		0.4 × MIC	
		PAE	SME	PA-SME	SME	PA-SME	SME	PA-SME	SME	PA-SME
18 (S)	0.25	0.6 (0.2–1.2)[d]	0.4 (0–0.8)	0.7 (0.4–1.2)	0.7 (0–1.5)	0.7 (0.2–1.3)	0.8 (0–1.8)	0.8 (0.2–1.5)	1.7 (0.8–2.7)	1.4 (0.9–2.1)
	0.5	2.6 (1.1–3.8)	0.1 (0–0.4)	3.1 (1.2–5)	0.2 (0–0.3)	3.3 (2.2–4.3)	0.4 (0–.7)	3.6 (2.2–4.8)	0.8 (0.6–0.9)	5 (3.6–6.5)
	1	9 (8.8–9.2)	0.4 (0–0.9)	9.7 (9.5–9.9)	0.3 (0.1–0.5)	14.6 (14.3–15)	0.8 (.5–1.2)	16 (15–17)	1.8 (1.2–2.5)	20.1 (16.9–23.3)
ATCC 49619 (I)	0.25	0.9 (0.4–1.1)	0.2 (0–0.2)	1.4 (0.7–2.5)	0.7 (0.3–1.3)	2.1 (1.4–2.9)	2.5 (2.2–2.9)	3.3 (3.3)	4.6 (3.8–5)	5.2 (4.6–5.7)
	0.5	4.1 (2.9–6.4)	0.4 (0–0.9)	5.2 (3–8.7)	1.7 (0–2.4)	8 (5.8–11.7)	2.6 (2–3.6)	8 (5.5–13)	6.8 (4.8–8.8)	>17.3 (7.9–>24)
	1	R[e]	R	R	R	R	R	R	R	R
24 (R)	0.25	0.4 (0–1.2)	0.4 (0–1.1)	1.1 (0.4–1.7)	1.4 (0.9–2)	1.3 (0.6–2)	1.5 (1.3–1.7)	1.8 (1.3–2.1)	2.9 (2.5–3.7)	3.6 (2.5–4.5)
	0.5	1.7 (1.5–1.9)	0.3 (0.2–0.5)	2.2 (1.9–2.4)	0.5 (0.4–0.6)	3 (2.2–3.5)	0.9 (0.6–1.1)	4.1 (3.7–4.3)	1.8 (1.1–2.2)	6.1 (5.3–7.2)
	1	7.4 (6.3–8.5)	0.1 (0–0.1)	10.4 (8.3–12.5)	0.2 (0–0.4)	>9 (9–>24)	0.7 (0.4–1)	>24 (>24)	0.8 (0.5–1)	>24 (>24)

[a] S, susceptible; I, intermediately susceptible; R, resistant.
[b] PAE was induced by 1 h of exposure.
[c] Mean (range) of three experiments, unless otherwise noted.
[d] Mean (range) of two experiments.
[e] R, rapid bactericidal activity; after exposure, the number of organisms was reduced to a level below the detectable range.

TABLE 2. PAEs, SMEs, and PA-SMEs of quinupristin-dalfopristin for staphylococci[a]

Strain (drug susceptibility)[b]	Mean (range) effect (h)								
	PAE[c]	0.1 × MIC		0.2 × MIC		0.3 × MIC		0.4 × MIC	
		SME	PA-SME	SME	PA-SME	SME	PA-SME	SME	PA-SME
S. aureus (Met^r Ery^s)	5.9 (5.4–6.1)	0 (0–0.2)	6.9 (6.6–7.1)	0.1 (0–0.3)	8.0 (7.8–8.2)	0.4 (0.3–0.6)	8.8 (8.6–9.0)	0.6 (0.5–0.7)	10.4 (10.1–10.6)
S. aureus (Met^r Ery^s)	7.0 (6.7–7.3)	0 (0–0.1)	8.1 (7.9–8.3)	0.4 (0.1–0.8)	9.2 (8.9–9.5)	0.7 (0.4–0.9)	10.7 (10.4–11.1)	1.1 (0.8–1.2)	11.2 (10.1–12.7)
S. aureus (Met^r Ery^s)	4.6 (4.1–5.1)	0	5.6 (5.0–6.0)	0	7.5 (6.7–8.7)	0.2 (0–0.4)	8.0 (7.6–8.5)	0.7 (0.5–1.5)	9.4 (9.2–9.5)
S. aureus (Met^r inducibly Mac^r)	5.7 (5.2–6.3)	0	6.4 (5.5–6.8)	0.2 (0.1–0.3)	7.3 (6.6–7.9)	1.0 (0.8–1.3)	8.6 (7.7–9.3)	1.3 (1.2–1.6)	10.4 (8.8–11.6)
S. aureus (Met^r inducibly Mac^r)	5.5 (5.1–5.8)	0.1 (0–0.2)	6.5 (6.0–7.1)	0.8 (0.3–0.9)	7.7 (7.2–8.4)	1.2 (1.1–1.4)	8.9 (8.5–9.8)	1.5 (1.2–1.8)	10.9 (9.8–12.9)
S. aureus (Met^r constitutively Mac^r)	2.3 (1.9–2.7)	0.4 (0.3–0.6)	3.3 (3.1–3.5)	1.1 (0.9–1.4)	4.8 (4.2–5.2)	2.5 (1.6–3.2)	7.1 (6.6–7.5)	7.8 (6.3–9.0)	9.7 (8.5–10.7)
S. aureus (Met^r constitutively Mac^r)	2.5 (2.2–2.9)	0	3.8 (3.2–4.3)	0.8 (0.2–1.4)	5.5 (3.9–7.3)	3.1 (2.4–3.5)	6.6 (5.4–8.8)	7.3 (6.4–8.2)	10.4 (9.3–12.5)
Coagulase-negative staphylococci (Met^s)	4.7 (4.2–5.3)	0.3 (0.1–0.5)	4.9 (4.6–5.4)	0.4 (0.2–0.6)	5.3 (4.9–6.0)	0.4 (0.2–0.6)	5.6 (5.3–6.0)	0.8 (0.5–1.2)	6.6 (6.5–6.9)
Coagulase-negative staphylococci (Met^s)	5.3 (4.6–5.8)	0.3 (0.1–0.4)	5.7 (4.8–6.3)	0.2 (0–0.4)	6.0 (4.6–6.9)	0.3 (0–0.6)	6.5 (5.4–7.1)	0.8 (0.3–1.2)	6.7 (6.0–7.1)
Coagulase-negative staphylococci (Met^r)	4.0 (2.7–5.8)	0	4.0 (2.9–5.3)	0.1 (0–0.3)	4.6 (3.0–6.0)	0.3 (0–0.7)	4.6 (3.4–6.0)	0.3 (0–0.7)	5.9 (5.1–7.3)
Coagulase-negative staphylococci (Met^r)	4.0 (3.6–4.4)	0	4.1 (3.5–4.5)	0.1 (0–0.4)	4.9 (4.1–5.6)	0.7 (0.4–1.3)	5.1 (4.4–5.6)	0.4 (0–0.6)	6.4 (5.9–7.3)

[a] See Table 1, footnote *a*.
[b] Met, methicillin; Ery, erythromycin; Mac, macrolide; ^{s}, susceptible; ^{r}, resistant.
[c] Initial exposure concentration, 10 times the MIC.

TABLE 3. PAEs, SMEs, and PA-SMEs of quinupristin-dalfopristin for vancomycin-susceptible and -resistant *E. faecium* strains

Phenotype[a]	Exposure concn (× MIC)	Mean (range) effect (h)								
		PAE	0.1 × MIC		0.2 × MIC		0.3 × MIC		0.4 × MIC	
			SME	PA-SME	SME	PA-SME	SME	PA-SME	SME	PA-SME
Van^s	10	8.6 (8.3–8.9)	0.3 (0–0.5)	11.2 (10.3–12.5)	0.3 (0–0.6)	>12	1.0 (0.7–1.5)	>12	3.6 (2.0–4.4)	>12
	0.25	8.4 (8.1–9.0)	0	8.5 (8.1–9.2)	0	9.3 (9.0–9.5)	0	9.8 (9.5–10.2)	0.3 (0–0.5)	10.7 (10.3–11.2)
Van^s	10	8.4 (7.7–8.8)	0.4 (0.3–0.5)	11.8 (11.3–12.5)	0.6 (0.5–0.7)	>12	2.1 (1.5–2.7)	>12	9.0 (8.3–9.5)	>12
	0.25	8.6 (8.0–9.5)	0.2 (0–0.6)	8.9 (8.2–9.7)	0 (0–0.1)	9.5 (9.0–9.9)	0 (0–0.1)	9.6 (9.1–10.4)	0.1 (0–0.2)	10.9 (10.7–11.4)
Van^r		2.5 (2.0–2.8)	0.1 (0–0.4)	2.8 (2.1–3.5)	0.4 (0.1–0.7)	3.4 (3.0–3.8)	1.0 (0.6–1.2)	4.5 (4.1–5.2)	3.1 (2.5–3.8)	5.6 (4.6–6.5)
Van^r		2.7 (2.4–3.1)	0.9 (0.3–2.0)	3.4 (3.0–3.7)	1.0 (0.3–1.7)	4.3 (3.8–4.8)	2.4 (1.7–3.5)	5.4 (4.6–6.2)	4.3 (3.7–4.8)	7.1 (6.3–8.7)

[a] Van^r, vancomycin resistant; Van^s, vancomycin susceptible.

in this study suggest that quinupristin-dalfopristin can be administered intermittently and support twice or three times daily dosing for infections caused by gram-positive cocci.

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