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Postantibiotic Effects of Telavancin against 16 Gram-Positive Organisms[▽]

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The in vitro postantibiotic effects (PAEs), postantibiotic sub-MIC effects (PA-SMEs), and sub-MIC effects of telavancin were determined for 16 gram-positive organisms. Telavancin staphylococcal, streptococcal, and enterococcal PAE ranges were 0.9 to 3.9 h, 0.4 to 6.7 h, and 0.3 to 2.2 h, respectively. The PA-SME ranges (0.4 times the MIC) for staphylococci, streptococci, and enterococci were 6.7 to >10.7 h, >10.7 to >11.0 h, and >10 to >10.8 h, respectively. The extended PAE of telavancin, together with its long elimination half-life in humans, supports once-daily dosing for this investigational drug.

The postantibiotic effect (PAE) is a pharmacodynamic parameter that may be considered in choosing antibiotic dosing regimens. It is defined as the length of time that bacterial growth is suppressed following brief exposure to an antibiotic (1, 3, 4). Odenholt-Tornqvist and coworkers (10, 11) have suggested that during intermittent dosage regimens, suprainhibitory levels of antibiotic are followed by subinhibitory levels that persist between doses and have hypothesized that persistent subinhibitory levels could extend the PAE. The effect of sub-MICs on growth during the PAE period has been defined as the postantibiotic sub-MIC effect (PA-SME), representing the time interval that includes the PAE plus the additional time during which growth is suppressed by sub-MIC. In contrast to the PA-SME, the sub-MIC effect (SME) represents the direct effect of subinhibitory levels on cultures which have not been previously exposed to antibiotics (10, 11).

Telavancin is an investigational bactericidal lipoglycopeptide antibiotic that possesses potent activity against gram-positive pathogens, including those which display lower susceptibility to vancomycin (5–8, 12, 14). Telavancin exerts its antimicrobial effects through a multifunctional mechanism that includes inhibition of cell wall synthesis and disruption of the functional integrity of the bacterial membrane (7, 8). In the current study, we have examined the in vitro PAEs, PA-SMEs, and SMEs of telavancin against 16 gram-positive bacteria.

The organisms included 11 strains of methicillin-resistant *Staphylococcus aureus* (MRSA), including 4 vancomycin-intermediate (VISA) isolates, 2 heterogeneous VISA isolates, and 1 vancomycin-resistant (VRSA) strain. All vancomycin-intermediate and -resistant MRSA strains were isolated from patients at Hershey Medical Center. Additionally, one *Streptococcus pyogenes*, one *Streptococcus agalactiae*, two vancomycin-susceptible *Enterococcus faecalis*, and one vancomycin-susceptible *Eenterococcus faecium* isolate were tested. Telavancin susceptibility powder was obtained from Theravance, Inc., and solubilized as recommended by the manufacturer.

Telavancin MICs were determined by macrodilution procedures (2). The PAE was determined by the viable plate count method (1, 3, 4) using Mueller-Hinton broth (Difco Laboratories, Detroit, MI). The PAEs were induced by exposure to telavancin at 10 times the MIC for 1 h.

For PAE testing, tubes containing 5 ml broth with antibiotic were inoculated with approximately 5×10^6 CFU/ml. Inocula were prepared by suspending colonies from an overnight blood agar plate in broth according to the direct colony suspension method (2). 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 period, cultures were diluted 1:1,000 in broth to remove the antibiotic by dilution. Removal of the antibiotic was confirmed by comparing the growth curve of a control culture containing no antibiotic to another containing telavancin at 0.001 the exposure concentration (10 times the MIC).

Viability counts were determined before exposure and immediately after dilution (0 h) and then every 2 h until the turbidity of the tube reached a no. 1 McFarland standard. The PAE was defined by the equation $PAE = T - C$; where T is the time required for viability counts of an antibiotic-exposed culture to increase by 1 $\log_{10}$ above counts immediately after dilution and C is the corresponding time for growth control.

In cultures designated for PA-SME, the PAE was induced as described above, after exposure to 10 times the MIC (see above). After 1:1,000 dilution, cultures were divided into four tubes. To three tubes, telavancin was added to produce final subinhibitory concentrations of 0.2, 0.3, and 0.4 times the MIC. The fourth tube did not receive antibiotic. Viability counts were determined before exposure, immediately after dilution, and then every 2 h until their culture turbidities reached a no. 1 McFarland standard. Cultures designated for SME were treated the same as for PA-SME testing except that the PAE was not induced. The formulas used to calculate the PAE, PA-SME, and SME have been previously described (13).

The PA-SMEs and SMEs were measured in two separate experiments (done twice, each starting with a new inoculum). For each experiment, viability counts ($\log_{10}$ number of CFU/ml) were plotted against time, and results were expressed as two separate values (Table 1).

Telavancin MICs ranged from 0.06 to 0.5 μg/ml for all 16 isolates. For the MRSA isolates, telavancin MICs ranged from

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TABLE 1. PAEs of telavancin for 16 strains

Strain description	MIC (μg/ml)	PAEs[b] (h)	Duration of effect (h)[a]					
			0.2 ×MIC		0.3 ×MIC		0.4 ×MIC	
			SMEs[c]	PA-SMEs[d]	SMEs	PA-SMEs	SMEs	PA-SMEs
MRSA								
Vancomycin susceptible								
ATCC 33591	0.25	1.5, 2.0	0.3, 0.3	7.7, 8.0	1.4, 1.4	>10.0, >10.3	2.3, 3.5	>10.0, >10.3
SA 1130	0.12	1.4, 1.6	0, 0.4	5.4, 5.8	2.0, 4.4	10.0, >10.5	6.5, 6.9	>10.0, >10.5
SA 1307	0.12	1.1, 1.6	1.1, 1.0	6.0, 6.4	2.6, 3.1	>10.5, >10.6	6.3, 6.5	>10.5, >10.6
SA 1316	0.12	1.8, 2.0	0.7, 1.1	2.9, 3.1	5.1, 5.2	5.4, 5.6	6.0, 6.1	>10.7, >10.6
Heterogeneous vancomycin intermediate								
SA 618	0.12	1.7, 2.4	0.3, 0.8	5.7, 6.5	1.5, 1.6	8.3, 9.8	2.3, 4.3	10.3, >10.3
SA 873	0.12	1.2, 1.6	0, 0.3	3.6, 4.0	0.5, 0.8	4.8, 6.0	1.0, 1.8	6.7, 7.0
Vancomycin intermediate								
SA 555	0.5	3.4, 3.9	0.3, 0.3	5.9, 6.0	1.7, 2.3	10.3, >10.6	4.3, 5.4	>10.3, >10.6
SA 770	0.25	1.6, 2.3	0.7, 0.8	3.8, 5.0	0.8, 1.8	6.3, 8.3	0.8, 1.9	9.6, >10.7
SA 1287	0.5	1.2, 1.8	0, 0.3	5.1, 5.2	0.4, 0.7	8.6, 10.0	0.8, 1.2	>10.3, >10.0
SA 1984	0.25	0.9, 1.4	1.0, 1.0	6.8, 8.6	2.6, 3.0	>10.0, >10.6	10, 10.6	>10.0, >10.6
Vancomycin resistant								
SA 510	0.5	1.3, 2.0	1.9, 2.5	5.6, 5.8	2.3, 3.1	6.0, 6.6	3.6, 5.0	8.1, 8.8
Streptococcus pyogenes HMC 414	0.06	6.1, 6.7	0,0	8.7,10.7	0, 0.4	>10.7, >10.7	0.4, 0.7	>10.7, >10.7
Streptococcus agalactiae HMC 5	0.12	0.4, 1.0	0.2, 0.4	0.8, 2.1	2.1, 2.7	4.7, 6.2	>10.7, >11.0	>10.7, >11.0
Enterococcus faecalis ATCC 29212	0.25	0.3, 0.7	0.8, 0.7	5.3, 5.8	2.0, 2.8	>10.7, >10.8	3.6, 4.0	>10.7, >10.8
Enterococcus faecalis HMC 571	0.25	1.5, 2.2	0.1, 0.6	3.9, 5.1	2.6, 3.2	7.2, 7.6	9.6, 10.0	>10.6, >10.8
Enterococcus faecium HMC 588	0.12	1.2, 1.6	1.2, 1.8	1.9, 2.2	7.2, 7.7	8.9, 9.3	8.8 9.9	>10.0, >10.5

[a] Values are those obtained from two separate experiments.
[b] Strains were exposed to 10 times the MIC of telavancin (see text) for 1 h at 35°C. The drug was removed by 1:1,000 dilution.
[c] Strains not previously exposed to telavancin.
[d] Strains previously exposed to telavancin.

0.12 to 0.5 μg/ml. MICs for the VISA and vancomycin-resistant *S. aureus* strains were slightly higher than those for the vancomycin-sensitive *S. aureus* and heterogeneous VISA strains, but all telavancin MICs were ≤0.5 μg/ml. Telavancin MICs for *S. pyogenes*, *S. agalactiae*, *E. faecalis*, and *E. faecium* ranged between 0.06 and 0.25 μg/ml (Table 1).

The duration of the PAEs for all strains varied from 0.3 h to 6.7 h. PA-SMEs generally lasted longer than PAEs for all strains tested and increased with the subinhibitory concentration of telavancin.

S. aureus PAEs were between 0.9 and 3.9 h, with a mean of 1.8 h. The PAEs and PA-SMEs did not differ by vancomycin susceptibility. At 0.4 times the MIC, the vancomycin-susceptible, -heteroresistant, -intermediate, and -resistant strains had mean PA-SMEs of >10.4 h, >8.6 h, >10.3 h, and 8.4 h, respectively (Table 1). The PA-SMEs tested at subinhibitory concentrations of 0.2, 0.3, and 0.4 times the MIC lasted longer than did PAEs plus SMEs for all *S.aureus* strains (Table 1).

For *S. pyogenes* and *S. agalactiae*, the mean PAEs were 6.4 and 0.7 h, respectively. For *S. pyogenes*, the PA-SMEs lasted longer than the PAE plus the SME at 0.2, 0.3, and 0.4 times the MIC and were all ≥8.7 h. PA-SMEs exceeded the PAE plus SME at 0.3 and 0.4 times the MIC for *S. agalactiae*, with mean values of 2.4 and ≥10.8 h, respectively.

For the two *E. faecalis* strains, the mean PAE was 1.1 h. The mean PA-SMEs at 0.2, 0.3, and 0.4 times the MIC were 5.0 h, >9.1 h, and >10.7 h, respectively. The *E. faecium* strain had a mean PAE of 1.4 h. At subinhibitory concentrations of 0.2, 0.3, and 0.4 times the MIC, the mean PA-SMEs were 2.0 h, 9.1 h, and 10.3 h, respectively.

Telavancin MICs were similar to those described previously (6, 7). Pace et al. (12) reported telavancin PAEs of 4 to 6 h when tested against three *S. aureus* strains. In that study, the PAE for *S. aureus* (ATCC 33591) was reported to be 6 h, after preexposure of the cultures to telavancin at the MIC (0.5 μg/ml) for 1 h at 37°C. However, in the current study, we found a slightly lower MIC (0.25 μg/ml) and shorter PAEs (1.5, 2.0 h), with a long PA-SME of ≥7.7 h for the same strain. The reasons for these discrepancies are not clear and require further investigation. The very long PA-SMEs found for *S. aureus* ATCC 33591 in our study suggest that the residual telavancin left after preexposure would have lengthened the PAE in the former study and may explain the findings of Pace et al. (12). The telavancin PAE, PA-SME, and SME values found in this study against *S. aureus* are similar to those reported by others for vancomycin (5, 9).

In the current study, all of the strains were preexposed to telavancin at 10 times the MIC, well below the clinical levels achievable in humans (14). Telavancin has a long half-life (>7.0 h), with ≥90% protein binding in human serum (14). When an antibiotic has a long half-life, PAE, and PA-SME, longer intervals between doses may be possible, because regrowth continues to be prevented when serum and tissue drug levels fall below the MIC (1). The PAE and PA-SME would be important only for organisms with elevated MICs, where plasma levels (at least of free drug) may fall below the MIC. At

the currently reported dosing regimen (10 mg/kg every 24 h) (15–17), the concentrations of telavancin in plasma would exceed the MICs for the strains in this study over the entire dosing interval. The long serum half-life and PA-SMEs found in this study support once-daily dosing of telavancin.

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