Postantibiotic Effect of DX-619 against 16 Gram-Positive Organisms

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The in vitro postantibiotic effects (PAEs), the postantibiotic sub-MIC effects (PA-SMEs), and the sub-MIC effects (SMEs) of DX-619 were determined for 16 gram-positive organisms. DX-619 pneumococcal, staphylococcal, and enterococcal PAE ranges were 1.7 to 5.0 h, 0.7 to 1.8 h, and 1.2 to 6.5 h, respectively. The PA-SME ranges (0.4×MIC) for pneumococci, staphylococci, and enterococci were 5.2 to >8.6 h, 2.1 to 8.3 h, and 4.9 to >10.0 h, respectively.

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 (1–4). Odenholt-Tornqvist and coworkers 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-MIC concentrations 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 concentrations. In contrast to the PA-SME, the SME measures the direct effect of subinhibitory levels on cultures which have not been previously exposed to antibiotics (7, 8).


DX-619 MICs were determined by macrodilution procedures (6). The PAE was determined by the viable plate count method (3), using Mueller-Hinton broth supplemented with 5% lysed horse blood when testing pneumococci. The PAE was induced by exposure to 10× the MIC of DX-619 for 1 h.

For PAE testing, tubes containing 5 ml broth with antibiotic were inoculated with approximately 5 × 10⁶ CFU/ml. Inocula were prepared by suspending growth from an overnight blood agar plate in broth. Growth controls with inoculum but no antibiotic to another containing DX-619 at 0.001 MIC were grown. At the end of the exposure period, cultures were divided into four tubes. Viability counts were determined before exposure and immediately after dilution (0 h) and then every 2 h until turbidity of the tube reached a no. 1 McFarland standard. The PAE was definded as follows: PAE = T – C, where T = time required for viability counts of an antibiotic-exposed culture to increase by 1 log₁₀ above counts immediately after dilution and C = corresponding time for growth control (3).
To three tubes, DX-619 was added to produce final subinhibitory concentrations of 0.2, 0.3, and 0.4× 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 turbidity reached that of a no. 1 McFarland standard. Cultures designated for SME were treated the same as for PA-SME testing, except the PAE was not induced.

PA-SME was defined as follows: \( \text{PA-SME} = T_p - C \), where \( T_p \) = time for cultures previously exposed to antibiotic and then reexposed to different sub-MICs to increase by 1 log_{10} above counts immediately after dilution and \( C = \) corresponding time for the unexposed control (7, 8). The SME was defined as follows: \( \text{SME} = T - C \), where \( T \) = time for the cultures exposed only to sub-MICs to increase 1 log_{10} above counts immediately after dilution and \( C = \) corresponding time for unexposed the control. The PA-SME and SME (7, 8) were measured in two separate experiments. For each experiment, viability counts (log_{10} CFU/ml) were plotted against time and the results are expressed as the mean of two separate assays using two separate inocula.

The DX-619 MICs were as follows: pneumococci, 0.004 to 0.03 g/ml; \( S. \) aureus, 0.004 to 0.25 μg/ml; \( E. \) faecalis, 0.03 to 0.25 μg/ml; and \( E. \) faecium, 0.125 to 0.25 μg/ml (Table 1).

MICs of the two quinolone-resistant \( S. \) pneumoniae and \( S. \) aureus were higher when compared to susceptible strains of the same genus (Table 1).

The PA-SMEs were longer than the PAEs for all strains tested and increased with subinhibitory concentration of DX-619.
For the seven pneumococci, the mean PAE was 3.5 h, ranging between 1.7 and 5.0 h. At 0.4× MIC, penicillin-susceptible, -intermediate, and -resistant strains and quinolone-resistant strains had mean PA-SMEs of >7.8 h, 8.2 h, 6.2 h, and 6.4 h, respectively (Table 1).

Staphylococcal PAEs were 0.7 to 1.8 h, with a mean of 1.2 h. Staphylococcal PAEs did not differ greatly in methicillin-susceptible (0.7 to 1.3 h) or -resistant (1.2 to 1.6 h) and quinolone-resistant (1.6 to 1.8 h) S. aureus strains. The PA-SME at 0.4× MIC (mean for all five strains, 4.4 h) was longer than PAEs plus SMEs in one of the two methicillin-susceptible strains, both methicillin-resistant strains, and the quinolone-resistant strain. For the two methicillin-resistant strains, an increased PA-SME was found in both strains (3.8 to 5.5 h) compared to the SME (0.5 to 2.1 h) at 0.4× MIC (Table 1).

For the two E. faecalis strains, the mean PAE was 2.0 h. At 0.4× MIC, the PA-SME values were 4.9 h to 7.5 h. By comparison, for the two E. faecium strains the mean PAE and PA-SME (0.4× MIC) were 6.0 and >10.0 h, respectively (Table 1).

DX-619, like other quinolones, exhibits rapid concentration-dependent bactericidal activity and long PAEs (9). In this study, DX-619 PAEs ranged from 0.7 to 6.5 h for all strains. The PAEs for S. aureus strains were generally shorter than those of the other strains tested. DX-619 produced PAE and PA-SMEs in two quinolone-resistant strains (S. pneumoniae and S. aureus) that did not differ greatly from those for sensitive strains. Long PA-SMEs were found for all strains and ranged from 1.7 to 10 h, 1.8 to >8.6, and 2.1 to >8.6 h at subinhibitory concentrations of 0.2, 0.3, and 0.4× MIC, respectively. These PA-SMEs may be more clinically relevant compared to the PAEs during intermittent dosage regimens, since suprainhibitory concentrations will be followed by exposure to subinhibitory concentrations in vivo. Longer intervals between doses may be possible when an antibiotic has a long half-life as well as a prolonged PAE and PA-SME, because regrowth continues to be prevented when serum and tissue levels fall below MICs (1, 2). The PAE and PA-SME would only be important for organisms with high MICs where serum levels (at least of free drug) would fall below the MIC. This would not occur with pneumococci and staphylococci with low MICs, and could be a problem for strains such as one of our methicillin-susceptible S. aureus strains with relatively short values. With these caveats, our results support once-daily dosing of DX-619, with possible twice-a-day dosing against methicillin-resistant S. aureus. These hypotheses must await further pharmacokinetic studies.

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REFERENCES