Letter to the Editor

Effects of Reduced Cation Supplement Recommendations (National Committee for Clinical Laboratory Standards) on Daptomycin Antistaphylococcal Activity

Daptomycin (formerly LY146032) is a new antimicrobial agent most appropriately described as a cyclic peptide with a lipophilic decanoyl tail or side chain (6, 8). This compound has a significant activity against gram-positive pathogens, including Staphylococcus spp., streptococci, Enterococcus spp., Listeria monocytogenes, and clinically important anaerobic bacteria such as Clostridium difficile (2, 4, 5, 7). Several authors have demonstrated a remarkable calcium ion-dependent daptomycin potency (2, 4, 5, 7). In many of these experiments limited numbers of strains were tested and/or the cationic concentrations were not relevant to current standardized broth susceptibility testing procedures (10).

The National Committee for Clinical Laboratory Standards (NCCLS) recently altered their recommendations for Mueller-Hinton broth (MHB) divalent cation content, principally based on the aminoglycoside studies reported by Barry et al. (3). Those studies did not address other ion-dependent antimicrobial susceptibility test results, e.g., with bacitracin, lipophilic polypeptides, polymyxins, and tetracyclines. Since daptomycin has a calcium-dependent bacterial membrane interaction that promotes a possible cytoplasm membrane peptidoglycan synthesis alteration (1, 8), it seems prudent to consider the effects of the recent NCCLS supplement recommendations on daptomycin broth MICs. In this letter I report the results of testing 587 staphylococcal strains in two types of cation-adjusted MHB media (9, 10). The broth microdilution trays were prepared by incorporating twofold dilutions of daptomycin (Eli Lilly Research Laboratories, Indianapolis, Ind.) into MHB (Difco Laboratories, Detroit, Mich.) having final divalent cation concentrations of (i) 50 mg of calcium and 25 mg of magnesium per liter (9) and (ii) 20 mg of calcium and 10 mg of magnesium per liter (10). The organisms tested included oxacillin-susceptible Staphylococcus aureus (148 strains), oxacillin-resistant S. aureus (275 strains), oxacillin-susceptible coagulase-negative Staphylococcus spp. (45 strains), and oxacillin-resistant coagulase-negative Staphylococcus spp. (119 strains). All coagulase-negative staphylococci (10 species) were recently isolated from clinical bacteremias, and the S. aureus strains came from blood and nosocomial wound infection cultures at 42 U.S. medical centers. Results with all species were very similar, and the data were merged for presentation. Oxacillin resistance (MIC, >2 μg/ml) was determined in 2% NaCl-supplemented MHB and confirmed by methicillin MICs and 1-μg oxacillin disk test results (9, 10).

Table 1 summarizes the daptomycin MIC results obtained with two levels of divalent cation supplementation (9, 10). As predicted from earlier experiments (2, 4, 5, 7), daptomycin was more active at the previously recommended higher calcium supplement concentration (9). Using the commonly reported MIC50 and MIC90 (MICs for 50 and 90% of strains tested, respectively) statistics, only the daptomycin MIC90 result was elevated from 0.5 to 1.0 μg/ml by lowering the calcium supplement level (10). In both media, daptomycin MICs were all ≤2.0 μg/ml, i.e., the susceptibility breakpoint MIC tentatively recommended in our earlier publication (7). A more sensitive statistical or reporting method to recognize the calcium effect on daptomycin activity was proposed by Schmidt (L. H. Schmidt, Antimicrob. Newsl. 4:1–8, 1987). This method would have indicated increases in MIC90 from 0.27 to 0.36 μg/ml and MIC90 from 0.45 to 0.85 μg/ml.

Our results showed a slight reduction (less than twofold) in daptomycin potency that would not significantly compromise the drug’s apparent spectrum of activity against contemporary staphylococcal isolates (Table 1). This minor activity shift was smaller than predicted from information reported by Andrews et al. (2) and Eliopoulos et al. (4), who used a more limited number of gram-positive organisms. Suggestions of calcium supplementation for daptomycin tests to a level of 100 mg/liter seem unfounded for the recognition of its utility against clinically important staphylococcal strains (2). Since the use of this new compound should be focused on therapy of serious staphylococcal infections, the data presented here from a large, geographically diverse sample of oxacillin-resistant strains appear to be very relevant to susceptibility breakpoint decision making. However, further studies with other gram-positive species (Enterococcus faecium and L. monocytogenes) for which daptomycin MICs are near the 2-μg/ml breakpoint are required to completely validate the effect of NCCLS divalent cation supplement recommendations for the lipophilic peptides.

LITERATURE CITED


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