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NOTES

In Vitro Activities of SCH27899 Alone and in Combination with 17 Other Antimicrobial Agents

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SCH27899, an everninomicin antibiotic, was tested for its in vitro activity against 718 bacterial isolates representing 27 species. The *Enterobacteriaceae* and nonenteric gram-negative bacilli were resistant to ≥8.0 μg/ml, but all others were inhibited by ≤1.0 μg/ml. When tested in combination with 17 other antimicrobial agents against 110 strains, SCH27899 demonstrated no significant antagonism or synergy. Consequently, combination therapy is not contraindicated.

SCH27899 is a parenteral oligosaccharide antibiotic belonging to the everninomicin class, first described in 1964 (10). Previous studies have shown SCH27899 to have good activity against gram-positive species, including methicillin-resistant staphylococci, vancomycin-resistant enterococci (VRE), and penicillin- resistant pneumococci (3–5, 9). It has been reported to be effective in the treatment of pneumococcal pneumonia in humans (7). Recent evidence suggests that its mechanism of antimicrobial activity is inhibition of protein synthesis (2), which is mediated by binding to the ribosomal protein L16 (1). This unique mechanism of action together with its exceptional spectrum of activity makes SCH27899 a drug of considerable interest for further study.

Because SCH27899 is primarily effective against gram-positive species, it is likely to be administered with other antimicrobial agents when mixed infections are known or suspected. The present study was designed to confirm the in vitro antibacterial spectrum of SCH27899 and to screen for possible antagonistic or synergistic effects of SCH27899 on the in vitro antimicrobial activities of 17 other antimicrobial agents.

A total of 718 bacterial isolates representing 27 species was tested for susceptibility to SCH27899. The species names and numbers of isolates are listed in Table 1. Of these isolates, 110 were selected for the drug interaction phase: 55 nonfastidious gram-negative bacilli, 5 *Enterococcus faecalis* isolates (2 VRE isolates), 5 *Enterococcus faecium* isolates (2 VRE isolates), 5 *Staphylococcus aureus* isolates (2 methicillin-resistant isolates), 5 *Staphylococcus epidermidis* isolates (2 methicillin-resistant isolates), 5 pneumococci (2 penicillin-resistant and 1 penicillin-intermediate isolate), 5 *Streptococcus pyogenes* isolates, 5 *Streptococcus agalactiae* isolates, 10 *Haemophilus influenzae* isolates (3 β-lactamase-positive isolates and 2 β-lactamase-negative and ampicillin-resistant isolates), and 10 *Moraxella catarrhalis* isolates (5 β-lactamase-positive isolates).

SCH27899 was provided by Schering Plough, Kenilworth, N.J. The 17 antimicrobial agents used in the interaction phase were procured from their respective U.S. manufacturers or from commercial sources and are listed in Table 2.

MICs were determined by the broth microdilution method for nonfastidious organisms and streptococci and by agar dilution for other fastidious species, following the procedures outlined by the National Committee for Clinical Laboratory Standards (6). The cation-adjusted Mueller-Hinton broth was supplemented with ca. 3% lysed horse blood when streptococci were tested: For agar dilution tests, the medium varied with the organism tested: Mueller-Hinton agar for *M. catarrhalis*, Mueller-Hinton agar supplemented with 5% defibrinated sheep blood for *Neisseria meningitidis*, GC agar supplemented with IsoVitaleX for *Neisseria gonorrhoeae*, and *Haemophilus* test medium for *H. influenzae*. Concentrations of SCH27899 tested were twofold dilutions ranging from 8.0 to 0.06 μg/ml. For the drug interaction phase, only broth microdilution tests were used. Concentrations of the drugs tested in the interaction phase are listed in Table 2. Each of the 17 antimicrobial agents was tested alone and in combination with SCH27899 at 0.025, 0.25, and 2.0 μg/ml. MICs in the presence of subinhibitory concentrations of SCH27899 that were more than fourfold above or below the MICs in the absence of SCH27899 were considered to indicate possible antagonism or synergy, respectively.

The in vitro activity of SCH27899 against 27 species, including many multiresistant strains, is summarized in Table 1. All gram-positive strains, as well as all *N. gonorrhoeae*, *N. meningitidis*, and *M. catarrhalis* strains, were inhibited by ≤1.0 μg of SCH27899 per ml. No difference in SCH27899 MICs for antibiotic-resistant and antibiotic-susceptible strains of the same species was observed. Against *H. influenzae*, the median MIC was 2.0 μg/ml and the MIC at which 90% of the strains were inhibited (MIC_{90}) was 4.0 μg/ml. SCH27899 MICs for *Enterobacteriaceae* and nonenteric gram-negative bacilli were all >8.0 μg/ml. The results of this phase of the study are consistent with those previously reported (4, 5, 9).

The limited pharmacokinetic data reported to date indicate that achievable serum levels are linearly proportional to dosage: doses of 1, 3, 6, and 9 mg/kg resulted in mean maximum concentrations of drug in serum of 8.5, 29.7, 55.7, and 84.3 μg/ml, respectively, in healthy volunteers (8). However, SCH27899 appears to be highly protein bound. We recently tested 107 gram-positive isolates in Mueller-Hinton broth and in a 50/50 mixture of pooled human serum and Mueller-Hinton broth. For individual strains, serum increased MICs 2- to 32-fold (average 12.4-fold) (data not shown). Although the achievable levels in serum are high, the effect of the protein binding on in

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TABLE 1. In vitro activities of SCH27899 against 718 clinical isolates

Organism	No. of isolates	SCH27899 MIC (μg/ml)			
		Range	MIC_{50}	MIC_{90}	Geometric mean
Enterococcus faecalis[a]	29	0.25–1.0	0.5	1.0	0.58
Enterococcus faecium[a]	31	0.25–0.5	0.5	0.5	0.40
Staphylococcus aureus (methicillin resistant)	27	0.5–1.0	0.5	1.0	0.55
Staphylococcus aureus (methicillin susceptible)	25	0.25–0.5	0.5	0.5	0.49
Staphylococcus epidermidis (methicillin resistant)	15	0.25–0.5	0.5	0.5	0.48
Staphylococcus epidermidis (methicillin susceptible)	12	0.5–1.0	0.5	1.0	0.59
Streptococcus pneumoniae[b]	16	≤0.06–0.12	≤0.06	0.12	0.08
Steptococcus pyogenes	5	≤0.06	≤0.06		≤0.06
Streptococcus agalactiae	5	0.12–0.12	0.12		0.12
Viridans group streptococci	10	≤0.06–0.5	0.12	0.5	0.19
Listeria monocytogenes	5	0.25–0.5	0.25		0.29
Corynebacterium jeikeium	4	≤0.06–0.12	0.12		0.11
Moraxella catarrhalis	119	0.12–1.0	0.5	1.0	0.53
Neisseria gonorrhoeae	120	≤0.06–0.12	≤0.06	0.12	0.07
Neisseria meningitidis	122	≤0.06–0.25	≤0.06	0.12	0.07
Haemophilus influenzae	118	0.5–>8.0	2.0	4.0	1.92
Enterobacteriaceae[c]	47	>8	>8	>8	>8
Nonenteric gram-negative bacilli[d]	8	>8	>8		>8

[a] Half the strains were vancomycin-resistant.
[b] Six strains were penicillin resistant (MIC > 1.0 μg/ml) and three strains were penicillin intermediate (MIC of 0.12 to 1.0 μg/ml).
[c] Included three strains each of *Citrobacter diversus*, *Klebsiella oxytoca*, *Proteus vulgaris*, and *Providencia rettgeri* and five strains each of *Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morganii*, and *Proteus mirabilis*.
[d] Included five *Pseudomonas aeruginosa* and three *Stenotrophomonas maltophilia* strains.

vitro antibacterial activity supports our conservative view that the susceptible MIC breakpoint should be no higher than ≤4.0 μg/ml (a level that is tentative until clinical data have been collected and pharmacokinetic studies have been completed).

Table 2 summarizes the effect of SCH27899 on the MICs of 17 other antimicrobial agents. For over 95% of on-scale results, the MIC of an antibiotic with added SCH27899 was within a twofold concentration of that of the antibiotic alone. There were five (0.7%) instances in which the MIC with SCH27899 differed more than fourfold from the MIC without it. Four of these indicated possible synergy, and one indicated possible antagonism. Two of the possible synergies were with ampicillin when methicillin-susceptible staphylococci were tested. The instance of possible antagonism occurred with fusidic acid. With 15 isolates, there was a 2-$\log_2$ increase in fusidic acid MICs when fusidic acid was combined with SCH27899. Nevertheless, the overall results strongly suggest that SCH27899 could be used therapeutically in combination with one or more of the 17 studied antibiotics without significant antagonism or synergy.

TABLE 2. Effect of SCH27899 on MICs of 17 antimicrobial agents

Antimicrobial agent	Range (μg/ml)	No. of isolates on-scale	No. of isolates (%) exhibiting a MIC difference with SCH27899[a]		
			±1 $\log_2$	±2 $\log_2$	>2 $\log_2$
Ampicillin	0.06–8.0	30	25	3	2 (S)[b]
Cefazolin	0.12–16	33	30	3	
Ceftriaxone	0.12–16	15	15		
Chloramphenicol	0.5–64	61	60	1	
Ciprofloxacin	0.06–8.0	29	29		
Clindamycin	0.03–4.0	28	28		
Erythromycin	0.03–4.0	32	32		
Fosfomycin	0.06–8.0	53	49	2	2 (S)[b]
Fusidic acid	0.12–16	43	27	15	1 (A)[b]
Gentamicin	0.06–8.0	78	78		
Imipenem	0.03–4.0	52	52		
Quinupristin-dalfopristin	0.06–8.0	55	55		
Rifampin	0.004–64	74	74		
Tetracycline	0.06–8.0	68	68		
Ticarcillin	1.0–128	36	34	2	
Trimethoprim-sulfamethoxazole	0.03/0.57–4/76	44	44		
Vancomycin	0.06–8.0	28	28		
Total		759	728 (95.9)	26 (3.4)	5 (0.7)

[a] Three concentrations of SCH27899 were combined with serial dilutions of each study drug, and the interactions with the concentrations just below the MIC of SCH27899 are shown here.
[b] S, synergy; A, antagonism.

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