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Postantibiotic Effect of Sanfetrinem Compared with Those of Six Other Agents against 12 Penicillin-Susceptible and -Resistant Pneumococci

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The postantibiotic effect (PAE) and postantibiotic sub-MIC effect (PAE-SME) of sanfetrinem were compared to those of penicillin G, amoxicillin, cefpodoxime, ceftriaxone, imipenem, and clarithromycin against four penicillin-susceptible, four intermediately susceptible, and four resistant pneumococci. The MICs of imipenem were the lowest against all of the strains (0.03 to 0.5 μg/ml), followed by those of sanfetrinem (0.016 to 1.0 μg/ml), amoxicillin and ceftriaxone (0.016 to 2.0 μg/ml), and cefpodoxime (0.03 to 8.0 μg/ml). High-level resistance to clarithromycin (MIC, >64.0 μg/ml) was seen in three selected strains. The PAEs of all of the oral β-lactams tested were similar for all of the strains, ranging from 1 to 6.5 h. The PAEs of ceftriaxone and imipenem ranged from 1 to 8 h, and those of clarithromycin ranged from 1 to 7 h. The mean PAEs of all of the β-lactams and clarithromycin were 2.8 to 4.3 and 2.5 h, respectively. PAE-SMEs could not be determined for all of the strains due to complete killing, especially at high subinhibitory concentrations. However, the overall pattern with all of the compounds tested was that PAE-SMEs were longer than PAEs. Measurable PAE-SMEs of sanfetrinem at the three subinhibitory concentrations (0.125, 0.25, and 0.5 times the MIC) were 2 to 7, 2 to 7, and 3 to 6 h, while those of amoxicillin and cefpodoxime were 1 to 7.5, 2 to 4, and 4 to 9 and 2 to 7, 4 to 7, and 4 to 6 h, respectively. Measurable PAE-SMEs of ceftriaxone and imipenem were 1 to 6.5, 2 to 9, and 2 to 9 and 1.5 to 6, 2 to 5.8, and 4 to 7.7 h, respectively. Measurable clarithromycin PAE-SMEs were 1 to 5, 1 to 5, and 1 to 6 h at the three concentrations.

The past decade has witnessed a dramatic worldwide increase in the incidence of pneumococci which are resistant to penicillin G and other β-lactam and non-β-lactam agents (1, 3, 4). A recent survey in the United States has reported that 360 (23.6%) of 1,527 clinically isolated pneumococci showed reduced susceptibility to penicillin (7). There is an urgent need for antimicrobials which can be used for oral therapy of otitis media and respiratory tract infections caused by penicillin-resistant pneumococci (3, 9, 11). Of the available β-lactams, the MICs of amoxicillin are the lowest, followed by those of cefuroxime and cefpodoxime, while the MICs of cefprozil, cefixime, cefetamet, and cefaclor are higher (2, 13, 14, 16, 21, 23, 25). Use of macrolides is limited by the increasing frequency of resistance, especially in intermediately and fully penicillin-resistant strains (7, 11), while older quinolones are limited by poor pharmacokinetics and are not approved for use in children (9, 11).

Sanfetrinem is the orally absorbed hexetil ester of the trinem GV 104326. The compound is stable when exposed to clinically relevant β-lactamases such as those produced by *Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter diversus*, *Proteus mirabilis*, *P. vulgaris*, *Morganella morganii*, *Providencia rettgeri*, *Haemophilus* spp., and *Moraxella catarrhalis*. The compound is active against *Enterococcus faecalis*, *E. faecium*, *Staphylococcus aureus*, streptococci, *Rhodococcus*-like species, and anaerobes (6, 10, 22, 24). Sanfetrinem has been shown to be more active against penicillin-resistant pneumococci than are the other available oral β-lactams tested, with MICs of 0.03, 0.5, and 1.0 μg/ml for 90% of the penicillin-susceptible, intermediate susceptible, and resistant strains tested, respectively (6, 24). Sanfetrinem was more effective than ciprofloxacin or cefpodoxime in resolving murine pneumonia caused by penicillin-resistant pneumococci (6). Additionally, in a model using penicillin-resistant pneumococci, sanfetrinem was highly effective in reducing the number of pneumococci isolated per lung while no response to amoxicillin or cephalosporins occurred (6).

Postantibiotic effect (PAE) is the term used to describe suppression of bacterial growth which persists after short exposure of organisms to antimicrobials. The term has become the accepted name for this phenomenon because it stresses that the effect is due to prior antimicrobial exposure rather than to persisting subinhibitory concentrations of the compound. PAE has a major clinical impact on antimicrobial dos-

TABLE 1. Antibiotic MICs for the strains tested in this study

Strain	Penicillin G	Sanfetrinem	Amoxicillin	Cefpodoxime	Ceftriaxone	Imipenem	Clarithromycin
149	0.06	0.016	0.06	0.25	0.06	0.06	0.016
153	0.06	0.03	0.03	0.25	0.03	0.06	0.03
18	0.016	0.03	0.03	0.03	0.016	0.03	512.0
21	0.03	0.03	0.016	0.03	0.016	0.06	512.0
118	1.0	0.25	1.0	8.0	0.25	0.25	0.03
471	0.125	0.03	0.125	0.25	0.06	0.06	1,024.0
357	0.25	0.03	0.06	0.5	0.06	0.06	0.03
227	0.125	0.016	0.06	0.25	0.06	0.06	0.03
455	2.0	0.5	2.0	4.0	1.0	0.5	0.5
158	2.0	1.0	2.0	8.0	2.0	0.5	0.03
167	2.0	1.0	2.0	8.0	2.0	0.5	0.06
135	2.0	1.0	2.0	8.0	2.0	0.5	0.03

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TABLE 2. PAEs of inhibitory and subinhibitory concentrations of the antibiotic compounds tested in this study[a]

Drug and strain (penicillin susceptibility)[b]	PAE[c] (h)	PAE-SME[d] (h)		
		0.125 × MIC	0.25 × MIC	0.5 × MIC
Sanfetrinem				
149 (S)	3.0	5.0	5.0	6.0
153 (S)	3.0	>24.0	>24.0	>24.0
18 (S)	2.0	>24.0	>24.0	>24.0
21 (S)	>24.0	>24.0	>24.0	>24.0
118 (I)	5.0	7.0	7.0	>24.0
471 (I)	1.25	2.7	3.0	>24.0
357 (I)	2.0	2.0	2.0	>24.0
227 (I)	1.0	2.0	2.0	4.0
455 (R)	5.5	5.0	5.0	>24.0
158 (R)	4.0	4.0	>24.0	>24.0
167 (R)	3.0	3.0	3.0	3.0
135 (R)	5.0	6.0	>24.0	>24.0
Penicillin G				
149 (S)	1.0	5.0	5.0	>24.0
153 (S)	3.0	>24.0	>24.0	>24.0
18 (S)	3.0	3.0	6.0	8.0
21 (S)	3.0	3.0	5.0	>24.0
118 (I)	5.0	7.0	>24.0	>24.0
471 (I)	3.0	>24.0	>24.0	>24.0
357 (I)	2.0	>24.0	>24.0	>24.0
227 (I)	1.0	>24.0	>24.0	>24.0
455 (R)	1.0	2.0	2.0	2.0
158 (R)	4.0	7.0	>24.0	>24.0
167 (R)	4.0	4.0	6.0	>24.0
135 (R)	6.0	6.0	>24.0	>24.0
Amoxicillin				
149 (S)	3.0	3.0	3.0	9.0
153 (S)	2.5	3.5	>24.0	>24.0
18 (S)	6.5	>24.0	>24.0	>24.0
21 (S)	1.5	1.5	2.5	>24.0
118 (I)	5.0	>24.0	>24.0	>24.0
471 (I)	3.0	3.0	3.0	>24.0
357 (I)	1.0	7.0	>24.0	>24.0
227 (I)	1.0	1.0	2.0	4.0
455 (R)	5.0	>24.0	>24.0	>24.0
158 (R)	4.0	>24.0	>24.0	>24.0
167 (R)	1.0	1.0	4.0	>24.0
135 (R)	5.5	7.5	>24.0	>24.0
Cefpodoxime				
149 (S)	5.0	6.0	6.0	6.0
153 (S)	2.0	4.0	>24.0	>24.0
18 (S)	6.0	>24.0	>24.0	>24.0
21 (S)	2.0	2.0	4.0	4.0
118 (I)	3.0	7.0	7.0	>24.0
471 (I)	3.0	3.0	>24.0	>24.0
357 (I)	1.0	>24.0	>24.0	>24.0
227 (I)	2.0	>24.0	>24.0	>24.0
455 (R)	4.8	5.0	>24.0	>24.0
158 (R)	2.0	>24.0	>24.0	>24.0
167 (R)	5.0	7.0	>24.0	>24.0
135 (R)	1.5	3.5	5.5	>24.0
Ceftriaxone				
149 (S)	3.0	5.0	9.0	>24.0
153 (S)	2.0	2.0	2.0	2.0
18 (S)	5.0	6.5	7.0	9.0
21 (S)	2.0	2.0	3.0	5.0
118 (I)	5.0	5.0	5.0	>24.0
471 (I)	3.0	>24.0	>24.0	>24.0
357 (I)	1.0	2.0	3.0	>24.0
227 (I)	1.0	1.0	2.0	>24.0
455 (R)	7.2	>24.0	>24.0	>24.0
158 (R)	2.0	2.0	2.0	>24.0
167 (R)	1.0	1.0	2.0	7.0
135 (R)	1.5	3.5	4.5	>24.0
Imipenem				
149 (S)	3.0	>24.0	>24.0	>24.0
153 (S)	5.0	4.0	5.8	6.0
18 (S)	7.5	>24.0	>24.0	>24.0
21 (S)	8.0	>24.0	>24.0	>24.0
118 (I)	6.0	5.0	5.0	7.7
471 (I)	3.0	1.5	>24.0	>24.0
357 (I)	1.0	5.0	5.0	>24.0
227 (I)	1.0	2.0	4.0	4.0
455 (R)	5.0	2.0	2.0	>24.0
158 (R)	2.0	5.0	>24.0	>24.0
167 (R)	4.0	4.0	4.0	6.0
135 (R)	6.0	6.0	>24.0	>24.0
Clarithromycin				
149 (S)	1.0	3.0	3.0	3.0
153 (S)	4.0	4.0	4.0	4.0
18 (S)	>24.0	>24.0	>24.0	>24.0
21 (S)	5.0	5.0	5.0	6.0
118 (I)	3.0	3.0	5.0	5.0
471 (I)	7.0	>24.0	>24.0	>24.0
357 (I)	1.0	5.0	5.0	5.0
227 (I)	1.0	2.0	4.0	5.0
455 (R)	1.0	4.0	4.0	4.0
158 (R)	2.0	2.0	2.0	2.0
167 (R)	1.0	1.0	1.0	1.0
135 (R)	1.5	2.0	2.0	2.0

[a] The values shown are means of two determinations.

[b] S, penicillin susceptible I, intermediately penicillin susceptible; R, penicillin resistant.

[c] Exposure was 2 h at 10 times the MIC (β-lactams) or 5 times the MIC (clarithromycin). The drug was removed by 1:1,000 dilution.

[d] For PAE-SME, strains were exposed to a drug at 10 times the MIC for 2 h, the drug was removed (as for PAE testing), and then the bacteria were exposed to the drug at 0.125, 0.25, or 0.5 times the MIC.

ing regimens. Drugs with no PAEs require more frequent administration than those that demonstrate a PAE (5). However, the PAE alone may not fully explain the effectiveness of intermittent antibiotic dosing since the sum of the time during which the concentration of most antimicrobials is above the MIC and the time of the PAE does not cover the entire dosing interval. Odenholt-Tornqvist et al. (17–19) have reported a very long period of growth inhibition when some bacteria in the postantibiotic phase were exposed to 0.3 times the MIC and proposed the postantibiotic sub-MIC (PAE-SME) phenomenon to at least partially explain the latter discrepancy.

In the current study, we compared the PAE and PAE-SME of sanfetrinem against four penicillin-susceptible, four intermediately susceptible, and four resistant pneumococci to those of five other β-lactams and clarithromycin.

MATERIALS AND METHODS

Bacteria. The organisms used in this study were all clinical strains isolated during the past 2 years. For susceptible strains, the penicillin MICs were ≤0.06 μg/ml, for intermediate strains, the MICs were 0.1 to 1.0 μg/ml, and for resistant strains, the MICs were ≥2.0 μg/ml. Strains were frozen at −70°C in double-strength litmus milk (Difco Laboratories, Detroit, Mich.) prior to testing.

Antimicrobials and broth microdilution MIC testing. Sanfetrinem was obtained from Glaxo Wellcome S.p.A., Verona, Italy. Other compounds were obtained from their respective manufacturers. Broth microdilution MICs were determined as recommended by the National Committee for Clinical Laboratory Standards (15), by using cation-adjusted Mueller-Hinton broth (MHB; Difco) supplemented with 5% lysed, defibrinated horse blood (Cleveland Scientific, Inc., Bath, Ohio). For MIC determinations, suspensions with a turbidity equivalent to that of a 0.5 McFarland standard were prepared by suspending growth

from sheep blood agar plates (BBL Microbiology Systems, Cockeysville, Md.) in 2 ml of sterile saline. Suspensions were further diluted 1:10 to obtain a final inoculum of 5×10^5 CFU/well. Trays were incubated for 20 h in ambient air at 37°C. *Streptococcus pneumoniae* ATCC 49619 and *Staphylococcus aureus* ATCC 29213 were included as quality control strains in each run.

Measurement of PAE. PAEs were determined by the viable plate count method (5), by using MHB supplemented with 5% lysed horse blood. The bacterial inoculum was prepared by suspending growth from an overnight Trypticase soy blood agar plate in broth. The broth was incubated at 35°C for 2 to 4 h in a shaking water bath until the turbidity matched a no. 1 McFarland standard (approximately 5×10^8 CFU/ml).

For PAE experiments, 5 ml tubes of broth containing the antibiotic concentration to be tested at 10 times the MIC (except for clarithromycin, which, for solubilization reasons, was used at 5 times the MIC) were inoculated with 50 μl of inoculum to provide 5×10^6 CFU/ml. Tubes were then vortexed and plated for viability count determinations. Growth controls with inoculum but no antibiotic were included with each experiment. Inoculated test tubes were then placed in a shaking water bath at 35°C for an exposure period of 2 h. At the end of the exposure period, cultures were diluted 1:1,000 in prewarmed broth to remove the antibiotic. An additional control culture containing bacteria and an antibiotic at a concentration of 0.01 times the MIC was prepared to confirm that the antibiotic was no longer bacteriostatic after dilution.

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. Viability count determinations were performed by preparing 10-fold dilutions of 0.1-ml aliquots from each tube in MHB and plating 0.1-ml volumes onto Trypticase soy–5% sheep blood agar plates. Recovery plates were inoculated for at least 72 h, and colony counts were performed on plates yielding 30 to 300 colonies.

The PAE was defined in accordance with Craig and Gudmundsson (5) as $PAE = T - C$, where T is the time required for the viability count of an antibiotic-exposed culture to increase by 1 $\log_{10}$ above the count observed immediately after dilution and C is the corresponding time for the growth control.

For each experiment, viability counts, expressed as $\log_{10}$ CFU per milliliter, were plotted against time. Results were expressed as the mean of two separate assays.

Determination of PAE-SME (12, 17–20). In cultures designated for PAE-SME determination, the PAE was induced as described above. Following 1:1,000 dilution in broth to remove the antibiotic, cultures were divided into four tubes. To three of these tubes, compounds were added to produce subinhibitory concentrations of 0.125, 0.25, and 0.5 times the MIC. The fourth tube did not receive an antibiotic and served as a growth control. All 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, as described above for the PAE.

The PAE-SME was defined, as described by Odenhalt-Tornqvist and coworkers (17), as $PAE\text{-}SME = T_{pa} - C$, where T_{pa} is the time required for a culture previously exposed to an antibiotic and then re-exposed to different sub-MICs to increase by 1 $\log_{10}$ above the count observed immediately after dilution and C is the corresponding time for the unexposed control.

Results were plotted as described above for PAE results and expressed as the mean of two separate assays.

RESULTS

Microdilution MICs of all of the strains tested are presented in Table 1. As can be seen, the MICs of all β-lactams increased with those of penicillin G. The MICs of imipenem were the lowest against all of the strains (0.03 to 0.5 μg/ml). Sanfetrinem (0.016 to 1.0 μg/ml) had the lowest MICs of all of the oral β-lactams tested, followed by amoxicillin (0.016 to 2.0 μg/ml) and cefpodoxime (0.03 to 8.0 μg/ml). Ceftriaxone MICs ranged from 0.016 to 2.0 μg/ml. High-level resistance to clarithromycin (>64.0 μg/ml) was seen in three selected strains.

Antibiotics at 0.01 times the MIC had no residual bacteriostatic activity. Results of PAE and PAE-SME testing are presented in Table 2. PAEs and PAE SMEs could not be determined for some strains, due to complete killing after drug exposure. For the purpose of this study, complete killing is designated in Table 2 as >24.0 h, which is longer than the maximum time for which cultures were incubated. As can be seen, the PAEs of all of the oral β-lactams tested ranged from 1 to 6.5 h. PAEs for ceftriaxone and imipenem ranged from 1 to 8 h, and those of clarithromycin ranged from 1 to 7 h. The arithmetic mean PAEs of the compounds tested were as follows: penicillin, 3.0 h; sanfetrinem, 3.2 h; amoxicillin, 3.3 h; cefpodoxime, 3.1 h; ceftriaxone, 2.8 h; imipenem, 4.3 h; clarithromycin, 2.5 h.

PAE-SMEs, especially at higher subinhibitory concentrations, were longer than PAEs. The measurable PAE-SMEs of sanfetrinem at the three subinhibitory concentrations used (0.125, 0.25, and 0.5 times the MIC) were 2 to 7, 2 to 7, and 3 to 6 h, while those of amoxicillin and cefpodoxime were 1 to 7.5, 2 to 4, and 4 to 9 and 2 to 7, 4 to 7, and 4 to 6 h, respectively. The measurable PAE-SMEs of ceftriaxone and imipenem were 1 to 6.5, 2 to 9, and 2 to 9 and 1.5 to 6, 2 to 5.8, and 4 to 7.7 h, respectively. The measurable clarithromycin PAE-SMEs were 1 to 5, 1 to 5, and 1 to 6 h at the three concentrations (Table 2). The arithmetic means of the measurable PAE-SMEs at the three subinhibitory concentrations were as follows: penicillin G, 4.6, 4.8, and 5.0 h; sanfetrinem, 4.1, 3.9, and 4.3 h; amoxicillin, 3.4, 2.9, and 6.5 h; cefpodoxime, 4.7, 5.6, and 5.0 h; ceftriaxone, 3.0, 3.9, and 5.7 h; imipenem, 3.8, 4.3, and 5.9 h; clarithromycin, 3.1, 3.5, and 3.7 h.

DISCUSSION

The results of this study show significant PAEs for sanfetrinem and all of the other compounds tested. In general, PAE-SMEs were longer than PAEs. Complete killing of organisms in PAE and PAE-SME experiments, especially at higher subinhibitory concentrations, could have been due to drug-induced lysis or extremely rapid killing during the PAE exposure period. After initial exposure in the PAE phase, pneumococci may be more susceptible to autolysis in the PAE-SME phase because autolysin inhibitors have been reduced. In every case, drug-free controls yielded growth and the results of two separate assays were identical. More studies are required to elucidate this phenomenon.

A median area under the curve of 6.7 μg · h/ml and a median maximum drug concentration in serum of 3.5 μg/ml at approximately 0.75 h were obtained following a 500-mg oral dose of sanfetrinem (as the hexetil ester) administered as an experimental suspension to humans. At this dose and with this formulation, the median half-life was 1.3 h (8).

Results of sanfetrinem susceptibility studies against penicillin-susceptible, intermediately susceptible, and resistant pneumococci indicate that this compound is a promising new agent for treatment of infections caused by these strains. Results of the current study, together with the above pharmacokinetic data, suggest that the compound may be administered twice daily due to the PAE, despite the drug's short half-life.

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