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In Vitro Activity and β-Lactamase Stability of a Monobactam, SQ 26,917, Compared with Those of Aztreonam and Other Agents

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SQ 26,917 is a monobactam antibiotic. Its in vitro activity was compared with those of aztreonam, cefotaxime, ceftazidime, and moxalactam. SQ 26,917, which contains a β-methyl configuration on the β-lactam ring, was similar in activity to aztreonam with the exception of greater activity against *Pseudomonas aeruginosa* isolates. SQ 26,917 had no activity against gram-positive isolates or anaerobic bacteria. It was not hydrolyzed by common plasmid and chromosomal β-lactamases.

The discovery of the monocyclic β-lactams opened the possibility of the synthesis of a large number of interesting β-lactam compounds which might differ in their in vitro activity or human pharmacology (1, 9, 15). Aztreonam was the first monobactam to be studied extensively with respect to its in vitro activity, human pharmacology, and clinical efficacy (8, 10, 12–14). Aztreonam contains an α-methyl group on the β-lactam ring. This group provides stability against β-lactamases and may, in some degree, contribute to the antibacterial spectrum of aztreonam (2, 3). SQ 26,917 is a monocyclic β-lactam which is a β-methyl compound (Fig. 1). We wished to determine the in vitro activity and β-lactamase stability of this agent and to compare its activity with those of other agents.

MATERIALS AND METHODS

SQ 26,917 and aztreonam were gifts from R. Sykes, E. R. Squibb & Sons, Inc. Other agents were gifts from their manufacturers: ceftazidime, Glaxo Inc.; cefotaxime, Hoechst-Roussel Pharmaceutical Co., Inc.; moxalactam, Lilly Research Laboratories.

Fresh dilutions of bacteria were prepared daily in either sterile medium or distilled water. All bacterial isolates were from our collection of β-lactamase-containing bacteria. They were known to be multiply resistant to antimicrobial agents. The isolates had been stored frozen or on agar slants. The presence of β-lactamase in the isolates had been determined by the use of the chromogenic cephalosporin, nitrocefin.

Antimicrobial activity was measured by an agar dilution method with Mueller-Hinton agar unless specified otherwise. A final inoculum of 10^5 CFU, prepared by a dilution of a fresh overnight broth culture, was applied to agar by a replicating spot device. Broth dilutions were performed with 10^5 CFU in 1-ml tubes. The plates or tubes were incubated at 35°C for 18 h. The minimal inhibitory concentration (MIC) was defined as the lowest concentration of antibiotic that inhibited the development of visible growth on agar or in broth. The minimal bactericidal concentration, determined by plating 0.1-ml amounts from clear 1-ml broth tubes onto blood agar plates, was defined as the lowest concentration of antibiotic at which no growth occurred after 24 h of incubation at 35°C. The susceptibilities of the streptococci were determined on Mueller-Hinton agar supplemented with 5% sheep blood. The susceptibilities of *Neisseria* and *Haemophilus* spp. were determined on chocolate Mueller-Hinton agar incubated in the presence of 5% CO_2. Anaerobic susceptibility was determined on brucella agar supplemented with sheep blood and vitamin K. The incubation of the anaerobic cultures was for 48 h in GasPak jars (BBL Microbiology Systems).

We performed synergy studies on agar, using serial twofold dilutions of both agents as previously published (6). A fractional inhibitory concentration index of <0.5 was considered synergy, and a fractional inhibitory concentration index of ≥ 2 was considered antagonism. The antibiotic disk placement technique has also been used to find antagonism (16).

We determined stability to β-lactamase by a spectrophotometric assay, using the change in absorbance at the absorption maximum of each substrate. The inhibition of hydrolysis was determined with either cephaloridine or nitrocefin as the substrate (7).

The β-lactamases used in these studies have been previously discussed (6, 10). The destruction of compounds was followed spectrophotometrically at the extinction maximum of the compounds; cephaloridine was used as the standard. Inhibition assays were performed with cephaloridine used as the substrate. The change in absorbance at 255 nm was followed spectrophotometrically for 10 min after the enzyme was added. Incubation was at 30°C in a water-jacketed spectrophotometer. The reaction mixture contained 0.5 ml of 0.2 mM cephaloridine plus 0.5 ml of 0.05 M potassium phosphate buffer (pH 7) as a control, and each sample contained 0.5 ml of the compound tested as an inhibitor at a concentration of either 0.2 or 0.02

TABLE 1. Comparative in vitro activities of SQ 26,917 and other agents[a]

Species (no.)	Agent	Range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
Escherichia coli (32)	SQ 26,917	<0.025–1.6	0.1	0.2
	Aztreonam	<0.025–0.2	≤0.025	0.1
	Ceftazidime	0.05–6.3	0.2	0.8
	Moxalactam	0.025–0.4	0.05	0.1
	Cefotaxime	<0.025–0.4	0.05	0.1
Klebsiella pneumoniae (31)	SQ 26,917	0.05–0.8	0.1	0.2
	Aztreonam	<0.01–0.2	0.05	0.1
	Ceftazidime	0.05–1.6	0.2	0.4
	Moxalactam	0.05–0.8	0.1	0.4
	Cefotaxime	0.05–0.8	0.1	0.2
Klebsiella oxytoca (8)	SQ 26,917	0.1–0.4	0.1	0.4
	Aztreonam	0.1–1.6	0.1	0.8
	Ceftazidime	0.2–0.4	0.2	0.4
	Moxalactam	0.1–0.4	0.2	0.4
	Cefotaxime	0.1–0.4	0.1	0.4
Enterobacter aerogenes (24)	SQ 26,917	0.1–>100	0.2	>100
	Aztreonam	0.025–25	0.1	12.5
	Ceftazidime	0.2–>100	0.4	50
	Moxalactam	0.1–25	0.2	6.3
	Cefotaxime	0.1–25	0.2	12.5
Enterobacter cloacae (44)	SQ 26,917	0.025–>100	0.2	50
	Aztreonam	0.025–>50	0.1	12.5
	Ceftazidime	0.05–>100	0.4	50
	Moxalactam	0.05–50	0.1	6.3
	Cefotaxime	0.1–50	0.1	50
Enterobacter agglomerans (7)	SQ 26,917	0.05–50	0.1	0.2
	Aztreonam	0.01–100	0.05	0.2
	Ceftazidime	0.1–3.1	0.2	0.4
	Moxalactam	0.05–100	0.05	0.4
	Cefotaxime	0.05–100	0.05	0.4
Salmonella sp. (including *S. typhi*) (24)	SQ 26,917	0.05–0.4	0.1	0.2
	Aztreonam	0.025–0.2	0.1	0.2
	Ceftazidime	0.2–12.5	0.8	6.3
	Moxalactam	0.1–0.4	0.1	0.2
	Cefotaxime	<0.025–0.1	<0.025	0.1
Shigella sp. (*S. flexneri* and *S. sonnei*) (24)	SQ 26,917	0.05–0.4	0.1	0.4
	Aztreonam	0.025–0.2	0.05	0.1
	Ceftazidime	0.1–6.3	0.2	6.3
	Moxalactam	0.1–0.4	0.1	0.2
	Cefotaxime	<0.025–0.2	0.05	0.2
Citrobacter diversus (13)	SQ 26,917	0.05–0.2	0.05	0.2
	Aztreonam	<0.01–0.4	0.025	0.1
	Ceftazidime	0.1–0.4	0.1	0.2
	Moxalactam	0.05–0.2	0.05	0.2
	Cefotaxime	<0.025–0.2	0.05	0.2
Citrobacter freundii (24)	SQ 26,917	0.1–50	0.1	12.5
	Aztreonam	0.01–12.5	0.1	6.3
	Ceftazidime	0.1–>100	0.4	50
	Moxalactam	0.1–12.5	0.2	6.3
	Cefotaxime	0.01–50	0.1	12.5
Serratia marcescens (30)	SQ 26,917	0.1–25	0.8	6.3
	Aztreonam	0.05–50	0.1	6.3
	Ceftazidime	0.1–6.3	0.8	3.1

TABLE 1—*Continued*

Species (no.)	Agent	Range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
	Moxalactam	0.2–>100	1.6	50
	Cefotaxime	0.1–50	1.6	50
Proteus mirabilis (20)	SQ 26,917	0.01	0.01	0.01
	Aztreonam	≤0.05–0.01	≤0.05	0.01
	Ceftazidime	0.05–0.1	0.05	0.1
	Moxalactam	0.05–0.2	0.1	0.2
	Cefotaxime	<0.025–0.1	0.05	0.1
Proteus vulgaris (11)	SQ 26,917	<0.01–0.8	0.01	0.05
	Aztreonam	<0.005–0.8	0.01	0.1
	Ceftazidime	0.05–50	0.1	0.8
	Moxalactam	0.05–12.5	0.1	0.2
	Cefotaxime	0.05–12.5	0.1	3.1
Morganella morganii (16)	SQ 26,917	0.25–6.3	0.2	3.1
	Aztreonam	≤0.01–0.8	≤0.01	0.2
	Ceftazidime	0.05–25	0.1	6.3
	Moxalactam	0.1–0.4	0.1	0.4
	Cefotaxime	0.1–25	0.4	6.3
Providencia stuarti (29)	SQ 26,917	<0.01–>100	0.025	0.05
	Aztreonam	<0.01–>100	<0.01	0.05
	Ceftazidime	0.1–12.5	0.2	0.8
	Moxalactam	0.05–	0.05	0.2
	Cefotaxime	<0.025–3.1	0.1	0.8
Providencia rettgeri (15)	SQ 26,917	0.025–0.2	0.025	0.1
	Aztreonam	<0.005–0.2	0.01	0.1
	Ceftazidime	0.2–1.6	0.4	1.6
	Moxalactam	0.05–0.2	0.05	0.1
	Cefotaxime	0.05–1.6	0.1	0.8
Pseudomonas aeruginosa (61)	SQ 26,917	0.2–>100	3.1	12.5
	Aztreonam	0.2–>100	6.3	25
	Ceftazidime	0.8–100	1.6	12.5
	Moxalactam	3.1–>100	12.5	50
	Cefotaxime	3.1–>100	25	>100
Pseudomonas maltophilia (15)	SQ 26,917	0.8–25	3.1	12.5
	Aztreonam	>100	>100	>100
	Ceftazidime	0.8–50	0.8	50
	Moxalactam	1.6–100	3.1	25
	Cefotaxime	1.6–>100	25	>100
Acinetobacter sp. (14)	SQ 26,917	>100	>100	>100
	Aztreonam	>100	>100	>100
	Ceftazidime	12.5–>100	12.5	>100
	Moxalactam	100–>100	100	>100
	Cefotaxime	12.5–>100	>100	>100

[a] All β-lactamase isolates were resistant to ampicillin.

mM. The difference in the rate of destruction of cephaloridine during the linear part of the reaction was recorded.

RESULTS

The comparative activities of SQ 26,917, aztreonam, ceftazidime, moxalactam, and cefotaxime are given in Table 1. All of the isolates used were resistant to ampicillin, and all *Enterobacter, Citrobacter, Serratia, Morganella, Providencia, Pseudomonas*, and *Acinetobacter* spp. were resistant to cefazolin as well. SQ 26,917 had excellent in vitro activity comparable to those of aztreonam, cefotaxime, ceftazidime, and moxalactam against *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Entero-*

TABLE 2. Comparison of activities of SQ 26,917, SQ 26,776, and ceftazidime against *P. aeruginosa*[a]

Strain	MIC (μg/ml) of:		
	SQ 26,776	SQ 26,917	Ceftazidime
A-14	3.1	0.8	0.8
A-15	0.4	1.6	1.6
A-16	25	25	25
A-17	25	25	25
A-18	50	25	25
A-20	>50	25	12.5
A-22	0.4	0.2	0.8
A-23	12.5	3.1	3.1
A-25	12.5	12.5	1.6
A-26	6.3	6.3	3.1
A-29	6.3	6.3	6.3
A-35	0.2	3.1	1.6
A-36	3.1	1.6	1.6
A-39	12.5	1.6	0.8

[a] All isolates were resistant to carbenicillin (MIC > 400 μg/ml), piperacillin (MIC > 400 μg/ml), and gentamicin (MIC > 25 μg/ml).

bacter agglomerans, Salmonella sp., *Shigella* sp., *Citrobacter diversus, Proteus mirabilis, Proteus vulgaris,* and *Providencia* sp. The 90% MIC (MIC at which the growth of 90% of the bacteria was inhibited) was ≤0.8 μg/ml for all of these species for all of the compounds, and no major differences existed between the compounds. Against some *Enterobacter cloacae, Enterobacter aerogenes,* and *Citrobacter freundii* strains, moxalactam was more active than the other agents. Individual isolates varied in their susceptibilities to the agents. Some isolates that were susceptible to SQ 26,917 and to aztreonam were resistant to moxalactam and vice versa.

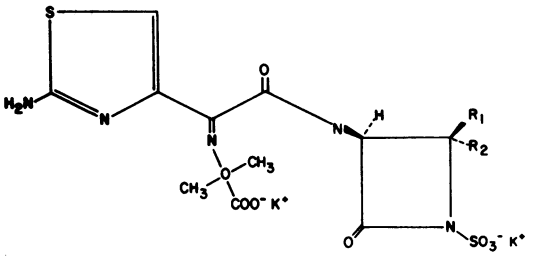

FIG. 1. Structure of aztreonam and SQ 26,917. In aztreonam, R_1 = H and R_2 = CH_3. In SQ 26,917, R_1 = CH_3 and R_2 = H.

Against *Pseudomonas* sp., SQ 26,917 was twofold more active than was aztreonam and had activity similar to that of ceftazidime (Tables 1 and 2). SQ 26,917, aztreonam, and ceftazidime were superior to cefotaxime and moxalactam against these *Pseudomonas aeruginosa* isolates, all of which were resistant to carbenicillin (MIC > 400 μg/ml). SQ 26,917 was the most active agent tested against *Pseudomonas maltophilia.* SQ 26,917 did not inhibit *Acinetobacter calcoaceticus.*

The agent was highly effective against *Neisseria gonorrhoeae* and *Haemophilus influenzae,* with 90% MICs of <0.1 μg/ml. The MICs of SQ 26,917 against other *Pseudomonas* spp.—*P. cepacia, P. fluorescens, P. stutzeri,* and *P. alcaligenes* (13 isolates)—ranged from 3.1 to >100 μg/ml.

TABLE 3. Stability of SQ 26,917 to β-lactamases

β-Lactamase	Source	Relative hydrolysis[a] of:				
		SQ 26,917	Aztreonam	Cefotaxime	Moxalactam	Cefoxitin
TEM-1[b]	*E. coli*	0	0	0	0	0
TEM-2[b]	*E. coli*	0	0	0	0	0
SHV-1[b]	*Klebsiella* sp.	0	0	0	0	0
OXA-1[b]	*E. coli*	0	0	0	0	0
OXA-2[b]	*E. coli*	0	0	0	0	0
OXA-3[b]	*E. coli*	0	0	0	0	0
K1	*Klebsiella* sp.	0	10	0	0	0
P99	*Enterobacter* sp.	0	1	0	0	0
PSE-1[b]	*Pseudomonas* sp.	0	0	0	0	0
PSE-2[b]	*Pseudomonas* sp.	2	15	10	5	5
PSE-3[b]	*Pseudomonas* sp.	0	0	0	0	0
PSE-4[b]	*Pseudomonas* sp.	0	0	0	0	0
Sabath-Abraham	*Pseudomonas* sp.	0	0	0	0	0
PC-1[b]	*S. aureus*	0	0	0	0	0
Type 1a[c]	*Citrobacter* sp.	0	0	0	0	0
Type 1a	*Morganella* sp.	0	0	0	0	0
Type 1a	*P. vulgaris*	0	0	74	0	0
Type 1a	*Serratia* sp.	0	0	0	0	0

[a] Based on a hydrolysis of cephaloridine equal to 100.
[b] Plasmid mediated.
[c] Richmond classification.

TABLE 4. Comparative inhibition of β-lactamases by different agents[a]

Enzyme	Concn of cephaloridine (M)	% Inhibition by:				
		SQ 26,917	Aztreonam	Cefotaxime	Moxalactam	Cefoxitin
TEM-1	10^{-4}	7.9	1.5	5.1	0	4
	10^{-5}	88.7	89.2	85.6	89.3	88.5
TEM-2	10^{-4}	0	11.3	0	0	1.1
	10^{-5}	88.9	91.7	90.4	86.5	90.4
P99	10^{-4}	100	98.6	98.4	100	99.3
	10^{-5}	100	100	99.2	100	100
Morganella sp.	10^{-4}	100	100	96.1	98.3	100
	10^{-5}	100	100	99.6	98.3	92.4
P. vulgaris	10^{-4}	0	21.2	—[b]	0	44
	10^{-5}	85	88.4	—	87.8	85.6
K1	10^{-4}	5.3	0	0.8	11.8	2.5
	10^{-5}	90	87.6	89.1	87.6	87.8

[a] The inhibitor was present at 10^{-5} M.
[b] —, Not done.

The activities of SQ 26,917, aztreonam, and ceftazidime against *Pseudomonas aeruginosa* isolates (Table 2) from patients who had been treated with ticarcillin, azlocillin, piperacillin, cefoperazone, cefsulodin, and moxalactam and from whom we had isolated resistant strains were studied. All of the isolates were ticarcillin and piperacillin resistant (MIC > 200 μg/ml) and gentamicin resistant (MIC > 12.5 μg/ml). Against these strains, the activities of SQ 26,917 and ceftazidime were similar and superior to that of aztreonam, and the MICs of SQ 26,917 were two- to fourfold lower than those of aztreonam.

SQ 26,917 did not inhibit (MIC > 50 μg/ml) *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus pyogenes, Streptococcus pneumoniae, Streptococcus faecalis, Streptococcus bovis, Listeria monocytogenes, Bacillus cereus, Bacillus fragilis, Fusobacterium varium, Clostridium perfringens, Eubacterium lentum,* peptococci, or peptostreptococci.

Effect of test conditions upon activity. The type of medium—Mueller-Hinton, brain heart infusion, Trypticase soy (BBL Microbiology Systems), and nutrient broths—used in agar assays caused no more than a single dilution change in the MICs for five isolates each of *Escherichia coli, Klebsiella pneumoniae, Morsanella morganii, Enterobacter cloacae, Serratia marcescens, Providencia* sp., and *Pseudomonas aeruginosa*. SQ 26,917 was equally active at pH 6, 7, and 8 against the above species, and the performance of anaerobic assays in GasPak jars (BBL) did not alter the MICs. At 10^{-7} CFU, the minimal bactericidal concentrations of these strains increased.

Combination of SQ 26,917 with other antibiotics. SQ 26,917 was combined with clindamycin, nafcillin, ampicillin, and metronidazole. The compounds were combined at equal concentrations. Ten strains of each bacterium were tested. In no instance did we find an antagonism of the activity of nafcillin, clindamycin, ampicillin, or metronidazole against aerobic gram-positive or anaerobic gram-negative bacteria. Conversely, the SQ 26,917 MICs against *Enterobacteriaceae* and *Pseudomonas* sp. were unchanged.

β-Lactamase stability and inhibitory activity. SQ 26,917 was as stable as aztreonam, ceftazidime, moxalactam, and cefoxitin against the major plasmid and chromosomal β-lactamases (Table 3). Slight destruction of SQ 26,917 by PSE-2 was noted, but it appeared somewhat more stable with the K1 enzyme than that of aztreonam. SQ 26,917 was also an effective inhibitor of chromosomal β-lactamases even when present at a 10-fold-lower concentration than the substrate, cephaloridine (Table 4). But like the other agents, it was a less effective inhibitor at low concentrations of the TEM-1 and TEM-2 enzymes, suggesting a lower affinity for these enzymes. Likewise, it was not as effective an inhibitor of the common all-purpose chromosomal K1 β-lactamase which is present in *Klebsiella* and some *Enterobacter* spp.

DISCUSSION

Monobactam antibiotics are the latest of a group of antibiotics with novel structures that have excellent in vitro activities (4, 8, 10, 13, 15). The first monobactam, aztreonam, inhibits the majority of gram-negative bacilli, including isolates resistant to ampicillin, carbenicillin, and cefazolin at concentrations below 1 μg/ml (8, 10). Aztreonam has a great affinity for penicillin-binding protein 3 and is bactericidal (13). Since an alteration in the configuration of substituents on the β-lactam ring has been shown to be able to markedly affect the activity of monobactams, we hoped that the β configuration of the methyl

group might alter the activity of SQ 26,917 (2, 3). This study shows that the β change made SQ 26,917 more active against some *Pseudomonas aeruginosa* isolates than is aztreonam, yielding activity virtually identical to that of ceftazidime (5). But the activity of SQ 26,917 was not improved against other species. Furthermore, the β configuration change did not provide any anti-anaerobic or anti-gram-positive coccal activity.

SQ 26,917 appears to be slightly more stable against attack by the K1 β-lactamase. It is also an effective inhibitor of chromosomal β-lactamases of the cephalosporinase type, Richmond Ia (11), but a less effective inhibitor of the common plasmid β-lactamase TEM. This study does not indicate that this compound would be a more useful agent clinically, since it is doubtful that the difference in the activities of SQ 26,917 and aztreonam against *Pseudomonas aeruginosa* would produce major clinical differences. Nonetheless, the study does demonstrate that small changes in structure can alter the activity of a compound against a particular species.

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