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Multicenter In Vitro Evaluation of SM-7338, a New Carbapenem

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A new carbapenem, SM-7338, was compared with imipenem, cefotaxime, and ceftazidime at five medical centers. Nearly 6,000 strains were tested by reference methods of the National Committee for Clinical Laboratory Standards, and SM-7338 inhibited the largest percentage of gram-negative bacilli. Its spectrum included all members of the family *Enterobacteriaceae* (99.7% were susceptible to ≤4 μg/ml), *Pseudomonas* spp. (but not *Xanthomonas maltophilia*), and *Acinetobacter* spp. The potency and spectrum of SM-7338 against the gram-positive organisms were less than those of imipenem and superior to those of ceftazidime. Only the enterococci and some oxacillin-resistant staphylococci were less susceptible to SM-7338 (MICs for 90% of isolates, ≥8 μg/ml). Organisms resistant to ceftazidime were generally susceptible to SM-7338 and imipenem (76%). However, for one-third of the imipenem-resistant gram-negative bacilli (MICs, >8 μg/ml), SM-7338 MICs were ≤4 μg/ml. Some endemic differences in patterns of SM-7338 activity against selected gram-negative species were found among some medical centers.

A wide variety of carbapenem drugs, including asparenomycins (7), carpetimycins (6), olivanic acids (2), pluracidomycins (17), PS-series compounds (11, 14, 15), and thienamycins (4, 5, 16), have been derived from strains of *Streptomyces* spp. Similar antimicrobial agents have also been produced by strains of *Serratia* and *Erwinia* spp. and by chemical modifications (10, 12). Although these compounds have possessed remarkably wide spectra of antimicrobial activity, only one clinically effective drug, imipenem-cilastatin, has been developed (4, 18). The reasons for rare clinical use of such compounds include toxicity, poor pharmacokinetics, adverse metabolism, and drug instability (10, 18). Imipenem seems to have overcome some of these drawbacks by the coadministration of the dehydropeptidase I inhibitor cilastatin (4, 5, 10, 18).

In this report, we summarize the findings of a multicenter in vitro study of SM-7338, a new carbapenem said to be more stable to human and animal dipeptidases (M. Sunagawa, H. Matsumara, T. Inoue, M. Fukasawa, and M. Kato, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 752, 1987; T. Tanio, H. Nouda, E. Tada, T. Kohzuki, M. Kato, M. Fukasawa, T. Okuda, and S. Kamidono, 27th ICAAC, abstr. no. 758, 1987). SM-7338 has been reported to have excellent activity against members of the family *Enterobacteriaceae*, *Pseudomonas aeruginosa*, *Branhamella catarrhalis*, *Haemophilus* spp., pathogenic *Neisseria* spp., *Staphylococcus* spp., streptococci, most enterococci, and beta-lactamase-producing anaerobic bacteria (J. R. Edwards, P. J. Turner, E. S. Withnell, and K. Nairn, 27th ICAAC, abstr. no. 755, 1987; J. R. Edwards and C. W. Wannop, 27th ICAAC, abstr. no. 754, 1987; T. Okuda, M. Fukasawa, T. Tanio, Y. Sumita, E. Tada, and T. Yukimatsu, 27th ICAAC, abstr. no. 757, 1987). Like other carbapenems, SM-7338 showed a high binding affinity for PBP 2, thus producing a primary morphological response of spherical cells (Y. Sumita, M. Fukasawa, and T. Okuda, 27th ICAAC, abstr. no. 756, 1987). In this study, we examined nearly 6,000 strains at six clinical microbiology laboratories by standardized susceptibility testing methods (8).

SM-7338 was supplied by Stuart Pharmaceuticals, Inc. (Wilmington, Del.). Drugs used for comparison were provided by the principal manufacturers in the United States.

Routine clinical isolates were tested at each of the five participating medical centers over a period of 45 to 60 days. A total of 5,866 isolates, including 2,911 members of the *Enterobacteriaceae*, 516 enterococci, 1,622 other gram-positive strains (mostly staphylococci), and 817 nonenteric gram-negative bacilli, were tested.

Each laboratory used the broth microdilution method of the National Committee for Clinical Laboratory Standards (8, 9), with cation-supplemented Mueller-Hinton medium and an inoculum of approximately 5×10^5 CFU/ml. Concurrent quality control procedures used the following recommended quality control strains: *Escherichia coli* ATCC 25922 (SM-7338 modal MIC, ≤0.06 μg/ml), *Staphylococcus aureus* ATCC 29213 (SM-7338 modal MIC, ≤0.06 μg/ml), *Enterococcus faecalis* ATCC 29212 (SM-7338 modal MIC, 4 μg/ml), and *P. aeruginosa* ATCC 29853 (SM-7338 modal MIC, 0.5 μg/ml). Quality control results of the facilities were within specified limits for all four study drugs, and the data were combined for this report. Strains demonstrating some resistance to one or more of three drugs, imipenem, SM-7338, and ceftazidime, were sent to The Clinical Microbiology Institute for further testing against a wider selection of antimicrobial agents; imipenem and SM-7338 MICs of ≥8 μg/ml and a ceftazidime MIC of ≥32 μg/ml were interpreted as indicating resistance (8, 9).

Table 1 summarizes the MIC results obtained by the broth microdilution method (8, 9) for 5,781 strains tested at five geographically separate medical centers. MIC ranges are not presented, since these generally included the entire dilution schedules used. SM-7338 was significantly more active than imipenem (2- to 16-fold) against the gram-negative organisms. However, imipenem appeared to be two- to fourfold more potent than SM-7338 against the gram-positive cocci,

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TABLE 1. Comparative antimicrobial activity of SM-7338 tested against 5,781 clinical isolates from five geographically separate medical centers

Organism (no. tested)	MIC (μg/ml)							
	SM-7338		Imipenem		Ceftazidime		Cefotaxime	
	50%	90%	50%	90%	50%	90%	50%	90%
Acinetobacter anitratus (78)	0.5	2	0.25	1	4	>16	8	>32
Pseudomonas aeruginosa (629)	0.5	4	1	8	2	>16	16	>32
P. cepacia (23)	2	8	8	>8	8	16	16	>32
P. fluorescens (16)	2	8	0.5	2	4	8	16	>32
Xanthomonas maltophilia (47)	>8	>8	>8	>8	16	>16	>32	>32
Citrobacter amalonaticus (14)	≤0.06	≤0.06	0.25	0.5	0.5	4	≤0.25	32
C. diversus (63)	≤0.06	≤0.06	0.25	0.5	0.25	2	≤0.25	0.5
C. freundii (120)	≤0.06	≤0.06	1	2	0.5	>16	≤0.25	>32
Enterobacter aerogenes (102)	≤0.06	≤0.06	1	2	0.25	>16	≤0.25	16
E. agglomerans (19)	≤0.06	≤0.06	0.25	0.5	0.25	2	≤0.25	1
E. cloacae (252)	≤0.06	0.12	0.5	2	0.5	>16	≤0.25	>32
Escherichia coli (1,252)	≤0.06	≤0.06	0.12	0.25	≤0.12	0.5	≤0.25	≤0.25
Klebsiella spp. (528)[a]	≤0.06	≤0.06	0.25	0.5	≤0.12	0.5	≤0.25	≤0.25
Morganella morganii (60)	≤0.06	0.25	2	4	≤0.12	8	≤0.25	4
Proteus mirabilis (284)	≤0.06	0.25	1	4	≤0.12	0.25	≤0.25	≤0.25
P. vulgaris (25)	≤0.06	0.12	2	4	≤0.12	1	≤0.25	>32
Providencia stuartii (20)	≤0.06	≤0.06	1	2	0.5	2	≤0.25	1
Salmonella enteritidis (16)	≤0.06	≤0.06	0.25	0.5	0.25	1	≤0.25	≤0.25
Serratia marcescens (101)	≤0.06	0.12	1	2	0.25	1	≤0.25	2
Shigella sonnei (28)	≤0.06	≤0.06	0.12	0.25	0.25	1	≤0.25	≤0.25
Enterococcus faecalis (223)	4	8	1	2	>16	>16	>32	>32
E. faecium (19)	>8	>8	4	>8	>16	>16	>32	>32
Enterococcus spp. (274)[b]	4	8	1	2	>16	>16	>32	>32
Streptococcus spp.								
Serogroup A (60)	≤0.06	≤0.06	≤0.06	≤0.06	≤0.12	0.25	≤0.25	≤0.25
Serogroup B (92)	≤0.06	0.25	≤0.06	≤0.06	1	1	≤0.25	≤0.25
Staphylococcus aureus (782)	≤0.06	0.25	≤0.06	≤0.06	8	16	1	1
S. epidermidis (261)	0.5	8	0.12	4	8	>16	2	16
S. haemolyticus (32)	>8	>8	1	>8	>16	>16	>32	>32
S. saprophyticus (13)	0.5	2	≤0.06	≤0.06	>16	>16	4	16
S. warneri (16)	4	>8	0.5	>8	>16	>16	2	16
CNS (332)[c]	0.5	8	≤0.06	2	16	>16	4	16

[a] Includes *K. oxytoca* (116 strains) and *K. pneumoniae* (412 strains). Susceptibility patterns for all species were identical.
[b] Without further identification as to species.
[c] CNS, Coagulase-negative *Staphylococcus* spp. without further identification as to species.

especially the *Enterococcus* species. All SM-7338 MICs for 50% of the enteric bacilli (MIC_{50}s) were ≤0.06 μg/ml, and the highest MIC_{90}s were 0.25 μg/ml for the *Morganella morganii* and *Proteus mirabilis* strains (99.7% of the *Enterobacteriaceae* were susceptible to SM-7338 at ≤4 μg/ml). The SM-7338 MIC_{90} for the *Pseudomonas aeruginosa* isolates was 4 μg/ml, and 85.9% of all nonenteric gram-negative bacilli were susceptible to SM-7338 (≤4 μg/ml). SM-7338 and imipenem were not active against the 47 strains of *Xanthomonas maltophilia* (MIC_{50}, >8 μg/ml), an observation contradictory to that reported from the United Kingdom (Edwards et al., 27th ICAAC).

Tests with the two comparison cephalosporins demonstrated that ceftazidime resistance has emerged at a slightly higher rate than has cefotaxime resistance. Examples include the following resistant (9) rates (as percentages) for ceftazidime and cefotaxime, listed by species: *Citrobacter freundii*, 21 and 12%; *Enterobacter aerogenes*, 20 and 7%; *Enterobacter cloacae*, 23 and 20%; and *Morganella morganii*, 5 and 4%. Also, among the *Escherichia coli* and *Klebsiella* spp. strains, twice as many strains were resistant to ceftazidime as were resistant to cefotaxime. These isolates may represent acquisition of the recently described CAZ or CTX plasmid (13). Ceftazidime was only slightly more active against the *Pseudomonas* spp. and *Acinetobacter* spp. strains but was markedly inferior to cefotaxime and to the carbapenems against the 1,436 staphylococci (ceftazidime resistance of 9 to 85%, depending on species). Results for the activities of cefotaxime and imipenem did not change from similar data generated by the same type of collaborative studies in 1982 through 1985 (1, 3).

A more limited number of strains from 13 other species or genus groups were tested against SM-7338 (Table 2). SM-7338 was very effective against all of these organisms, with an overall MIC_{50} of ≤0.06 μg/ml. Only two strains (*Staphylococcus hominis* and *Staphylococcus simulans*) for which the SM-7338 MIC was >8 μg/ml (resistant) were identified.

An endemic variation among the reporting medical centers for SM-7338 activity against some gram-negative species was observed (data not shown). MIC_{50}s for *Pseudomonas aeruginosa* ranged from 0.25 to 1 μg/ml (fourfold), and MIC_{90}s varied from 1 to 8 μg/ml. A similar variation (8- to 16-fold) was found for SM-7338 MIC_{90}s for *Proteus mirabilis*. Imipenem did not exhibit this phenomenon to the same extent, and all quality control results were within the acceptable range, which minimized the possibility of local error in use of reagents.

Only nine SM-7338-resistant *Enterobacteriaceae* were isolated and tested at the five collaborating facilities. These organisms included *Citrobacter* spp. (three strains), *Morganella morganii* (two strains), *Enterobacter aerogenes* (two strains), and *Serratia marcescens* (two strains). Some of

TABLE 2. Activity of SM-7338 against 85 strains from 13 additional species

Organism (no. tested)	MICs (μg/ml)[a]
Achromobacter spp. (5)	$\leq 0.06_1$, 0.12_2, 0.5_1, 1_1
Acinetobacter lwoffii (7)	$\leq 0.06_3$, 0.12_1, 0.25_1, 0.5_2
Aeromonas hydrophila (7)	$\leq 0.06_4$, 0.12_1, 0.25_1, 0.5_1
Alcaligenes spp. (5)	$\leq 0.06_5$
Bacillus spp. (5)	$\leq 0.06_1$, 0.5_2, 2_2
Escherichia hermanii (7)	$\leq 0.06_7$
Providencia rettgeri (9)	$\leq 0.06_6$, 0.12_1, 0.25_1, 1_1
Serratia liquefaciens (5)	$\leq 0.06_5$
Staphylococcus hominis (7)	$\leq 0.06_1$, 0.12_1, 0.25_2, 2_1, 4_1, $>8_1$
Staphylococcus simulans (8)	0.12_3, 0.25_1, 1_1, 2_1, 4_1, $>8_1$
Streptococcus bovis (6)	$\leq 0.06_4$, 0.12_1, 4_1
Streptococcus pneumoniae (8)	$\leq 0.06_7$, 0.12_1
Yersinia enterocolitica (6)	$\leq 0.06_2$, 0.12_1, 0.25_2, 1_1

[a] Subscript numbers are numbers of isolates for the indicated results.

these strains and other selected nonenteric gram-negative bacilli were sent to The Clinical Microbiology Institute for confirmation and special susceptibility testing. Each strain referred was resistant to one or more of the drugs imipenem (>8 μg/ml), SM-7338 (>8 μg/ml), and ceftazidime (>16 μg/ml). Table 3 summarizes the cross-resistance and -susceptibility data for SM-7338 in comparison with data for imipenem and ceftazidime. Among the 42 strains tested, 32 (76%) were ceftazidime resistant (8). SM-7338 and imipenem also failed to inhibit 5 and 16 of the strains, respectively. For six of 16 imipenem-resistant organisms, SM-7338 MICs were ≤4 μg/ml (susceptible). The five SM-7338-resistant organisms (MICs, >8 μg/ml) exhibited nearly complete cross-resistance to imipenem and ceftazidime. The susceptibility rates for other tested antimicrobial agents against these highly resistant organisms were as follows: cefotaxime, 41%; cefpirome, 62%; amikacin, 71%; tobramycin, 69%; ciprofloxacin, 81%; and ticarcillin-clavulanic acid, 18%. Only ticarcillin-clavulanic acid was less active than ceftazidime in vitro.

These results substantiate earlier findings of the excellent activity and spectrum of SM-7338. SM-7338 was the widest-spectrum compound tested against all gram-negative pathogens. However, imipenem had a minor advantage over SM-7338 against the enterococci (MIC_{90}s, 2 versus 8 μg/ml). Although SM-7338 and imipenem are both carbapenems, they seem to have differing activities against selected species, which results in some compromise of cross-resistance or -susceptibility correlations.

TABLE 3. Cross-resistance and -susceptibility analysis of 42 organisms gathered from the participating medical centers that were resistant to SM-7338 (>8 μg/ml), imipenem (>8 μg/ml), or ceftazidime (>16 μg/ml)[a]

Beta-lactam and MIC (μg/ml)	No. of strains with SM-7338 MIC (μg/ml) of:			
	≤2	4	8	>8
Imipenem				
≤4	23			
8		1	1	1
>8	2	4	6	4
Ceftazidime				
≤8	2	4	3	
16				1
>16	23	1	4	4

[a] Resistant strains were distributed by species as follows: *Pseudomonas aeruginosa*, 14; *Pseudomonas cepacia*, 4; *Flavobacterium* spp., 2; *Enterobacter cloacae*, 11; *Enterobacter aerogenes*, 5; *Citrobacter* spp., 4; and *Escherichia coli* and *Proteus mirabilis*, 1 each. Resistance was defined by standard M7-A or M100 (8, 9), with criteria for SM-7338 considered identical to those applied to the other carbapenem, imipenem.

Limited pharmacokinetic information indicates that SM-7338 is well tolerated and relatively stable to human dehydropeptidase I breakdown (data on file, Stuart Pharmaceuticals, Inc.). The elimination-phase serum half-life was found to be approximately 60 min. Peak concentrations in serum were equal to or higher than those of imipenem. Therefore, the imipenem susceptibility breakpoints applied to SM-7338 in this evaluation appear to be justified. This new carbapenem deserves further in vivo trials to determine its role in modern chemotherapy, especially for treatment of urinary tract infections without a dehydropeptidase I enzyme inhibitor coadministered drug (cilastatin) that is required for imipenem efficacy (18) and for minimizing nephrotoxity (10, 18).

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