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Compound A49759, the 3-*O*-Demethyl Derivative of Fortimicin A: In Vitro Comparison with Six Other Aminoglycoside Antibiotics

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O-Demethylfortimicin A (compound A49759) was tested against 445 bacteria, and the results were compared with those obtained with fortimicin A, amikacin, gentamicin, netilmicin, sisomicin, and tobramycin. A49759 was found to be active and bactericidal against the *Enterobacteriaceae*, nonfermentative gram-negative bacilli, and *Staphylococcus aureus*. A49759 was two- to fourfold more active than fortimicin A against most species tested, but generally fourfold less active than amikacin against this population of *Pseudomonas aeruginosa* (85% inhibited at ≤16 μg of amikacin per ml and 85% inhibited at ≤64 μg of A49759 per ml). Only amikacin and A49759 were resistant to most aminoglycoside-inactivating enzymes and also had significant antipseudomonal activity. Amikacin was inactivated by aminoglycoside 6'-acetyltransferase, and A49759 was inactivated by aminoglycoside 3-acetyltransferase. The minimal inhibitory concentrations of all tested aminoglycosides were increased by augmenting the inoculum size.

Several recent reports have described the in vitro antimicrobial activity of the pseudodisaccharide aminoglycoside antibiotics (4–8, 10, 11, 13, 14). Among these new compounds, the fortimicin group has been most extensively tested against recent clinical isolates (7). Numerous chemical and natural modifications of fortimicin have been presented (6, 8, 10, 14, 15). Fortimicin aminoglycosides are generally resistant to inactivating enzymes (6, 10, 13), but lack significant inhibitory activity against pseudomonads (6, 7). In recently presented abstracts no ototoxicity and very low renal toxicity for fortimicin A in the animal models were described (C. L. Yang, B. Buratto, S. B. Lehrer, I. A. Heyman, and J. L. Emerson, Prog Abstr. Inter. Cong. Chemother. 11th, and Intersci. Conf. Antimicrob. Agents Chemother. 19th, Boston, Mass., abstr. no. 774, 1979; R. E. Brummett, K. E. Fox, T. Bendrick, D. Himes, and R. Davis, 19th ICAAC, abstr. no. 776; E. T. Kimura, S. Tekeli, I. P. Lewkowski, K. R. Majors, and J. W. Kesterson, 19th ICAAC, abstr. no. 777).

The *O*-demethyl derivative of fortimicin A, compound A49759, has been synthesized by Abbott Laboratories, North Chicago, Ill. (9) that exhibits a greater antimicrobial activity than does the parent compound, especially against *Pseudomonas aeruginosa*.

In this study we compared the activity of A49759 with those of fortimicin A, amikacin, gentamicin, netilmicin, sisomicin, and tobramycin against a wide variety of organisms including those with established mechanisms of aminoglycoside resistance. The minimal inhibitory concentrations (MICs) and the minimal lethal concentrations (MLCs) were compared, and the effects of differences in inoculum concentration and cations on the MICs were determined.

MATERIALS AND METHODS

Antibiotics. Antibiotic powders suitable for susceptibility tests were supplied as follows: A49759 and fortimicin A sulfate from Abbott Laboratories, North Chicago, Ill.; tobramycin from Eli Lilly & Co., Indianapolis, Ind.; gentamicin, netilmicin, and sisomicin from Schering Corp., Bloomfield, N.J.; and amikacin from Bristol Laboratories, Syracuse, N.Y.

Organisms. A total of 445 bacterial strains were collected by the three collaborating laboratories, and others were provided by T. L. Gavan, The Cleveland Clinic Foundation, Cleveland, Ohio; E. Hugh Gerlach, St. Francis Hospital, Wichita, Kans.; and P. C. Fuchs, St. Vincent Hospital, Portland, Oreg. The above isolates were typical clinical strains, except for the predominantly aminoglycoside-resistant *P. aeruginosa* population and 25 additional isolates tested having known aminoglycoside resistance mechanisms (7, 16).

Most of the isolates were tested in duplicate by two of the collaborating laboratories (Center for Disease Control and the University of California [Davis] Medical Center) in a manner previously reported (1, 16). The third laboratory (Kaiser Foundation) tested a more limited number to study the effect of inoculum

size on MICs and comparisons of MICs and MLCs. Very similar MICs were obtained at the participating institutions; thus, data were pooled.

Antibiotic susceptibility tests. MICs were determined by the broth microdilution method. The test trays were prepared commercially (Prepared Media Laboratory, Portland, Oreg.) with a single lot of Mueller-Hinton broth and were distributed to the testing laboratories. The broth was supplemented to 50 mg of calcium and 25 mg of magnesium per liter. These trays were stored at −20°C or below until inoculated. Before use the trays were thawed at room temperature (approximately 20 to 30 min) and inoculated with disposable inoculators delivering 5 μl of inoculum to each well. The final inoculum achieved was approximately 10^5 colony-forming units (CFU) per ml. For the testing of *Haemophilus influenzae* and fastidious streptococci including *Streptococcus pyogenes* and *Streptococcus pneumoniae*, the inoculum was standardized in Mueller-Hinton broth containing 5% lysed rabbit blood, and 0.1 ml of this adjusted cell suspension was added to each microdilution well, giving a final concentration of 10^5 CFU/ml. The MIC was recorded as the lowest concentration totally inhibiting grossly visible bacterial growth (clear well), after approximately 18 h of incubation at 35°C.

MLCs were determined for 70 organisms from nine bacterial genera by subculturing 5 μl from each microdilution well to a Trypticase soy agar (BBL Microbiology Systems, Cockeysville, Md.) plate with 5% sheep blood. The subculture was made with a multiple inoculum replicator onto an agar plate (150 by 100 mm). After 48 h of incubation, the endpoints were read as the lowest concentration yielding no more than 0.1% survivors (99.9% kill).

The effect of varying the inoculum concentrations on the MIC was studied with 60 rapid-growing facultative anaerobes and 10 *P. aeruginosa* isolates. Trays were inoculated to achieve final concentrations of 10^3, 10^5, and 10^7 CFU/ml. Comparisons of MICs and MLCs were made with results obtained with the inoculum of 10^5 CFU/ml.

RESULTS

The range and MICs inhibiting 50 and 90% of tested organisms (MIC 50 and MIC 90, respectively) for A49759 and six other aminoglycosides against the *Enterobacteriaceae* are shown in Table 1. A49759 was clearly equal to or superior to the parent compound, fortimicin A, in its antimicrobial activity against this organism population. Gentamicin, netilmicin, sisomicin, and tobramycin remained the most active against susceptible *Escherichia coli*, *Enterobacter* species, *Klebsiella pneumoniae*, and *Proteus mirabilis* at both the MIC 50 and 90 level. Because of a variety of resistance mechanisms (inactivating enzymes) found in the *Proteus vulgaris*, *Morganella* sp., *Providencia* sp., and *Serratia marcescens*, the fortimicin A compounds and amikacin were more active than other aminoglycosides against these bacteria. Amikacin, fortimicin A, and A49759 are resistant to most inactivating enzymes except 6′-*N*-acetyltransferase [AAC(6′)] for amikacin and 3-*N*-acetyltransferase-I [AAC(3)-I] for fortimicin A and A49759 (5, 12, 13). Netilmicin was also very active against the *Serratia* isolates.

Table 2 compares A49759 MICs of nonfermentative gram-negative bacilli and gram-positive cocci to those of six other aminoglycosides. The MIC 50 values of amikacin and A49759 were intermediate between fortimicin A (highest) and the other drugs tested against acinetobacters, *Pseudomonas aeruginosa* (Fig. 1) and other *Pseudomonas* species. Only 28% of the 80 *P. aeruginosa* isolates tested (16) were susceptible to gentamicin (≤4 μg/ml). Thus, only A49759 and amikacin appear to be significantly active at achievable serum drug levels. A49759 MICs against the gentamicin-susceptible *P. aeruginosa* isolates were generally lower than those of the gentamicin-resistant group.

The *H. influenzae* strains were inhibited by all drugs tested, with most MIC 90 results of ≤4 μg/ml. A49759 appears equally active against beta-lactamase-producing and -deficient isolates, e.g., MIC ranges of 1 to 4 μg/ml for enzyme-negative isolates and 2 to 4 μg/ml for enzyme-positive isolates. Like other aminoglycosides, A49759 was relatively inactive against *S. pyogenes* and *S. pneumoniae*. Enterococcus strains (data not shown) also had modal aminoglycoside MICs within the intermediate or resistant ranges. A49759 had modal MICs against the staphylococci comparable to those of gentamicin, netilmicin, sisomicin, and tobramycin. Only rare *Staphylococcus aureus* strains had A49759 MICs of >2 μg/ml.

A49759 was found to be bactericidal at concentrations close to that of the MIC (Table 3). Only two isolates (*P. aeruginosa* and *P. vulgaris*) had A49759 MLCs 4-fold or greater than the MIC; 93 to 97% of aminoglycoside MLCs were ≤2-fold greater than the MIC. All of the higher netilmicin MLC/MIC ratios were with *S. marcescens* strains.

The effect of increasing inoculum concentrations on the MIC 90 is shown in Table 4. Small MIC increases were found with all drugs when the inoculum density was raised from 10^3 to 10^5 CFU/ml. When a 10^7-CFU/ml inoculum was used, A49759 and the other aminoglycoside showed a variable MIC response ranging from no change to a 16-fold MIC increase as compared with MICs with an inoculum of 10^5 CFU/ml. A49759 MICs against *P. aeruginosa* and *S. aureus* were least affected by increasing the inoculum concentration.

Table 5 shows representative aminoglycoside MICs for 10 of 25 organisms known to have enzyme-mediated resistance or to be permeabil-

TABLE 1. *MIC ranges and MICs of seven aminoglycosides inhibiting 50 and 90% of Enterobacteriaceae*

Organism (no. of isolates)	Aminoglycoside	MIC range (μg/ml)	MIC 50 (μg/ml)	MIC 90 (μg/ml)
E. coli (25)	A49759	1.0–4.0	2.0	4.0
	Amikacin	1.0–8.0	2.0	4.0
	Fortimicin A	2.0–8.0	4.0	4.0
	Gentamicin	≤0.25–2.0	1.0	1.0
	Netilmicin	≤0.25–2.0	0.5	1.0
	Sisomicin	≤0.25–1.0	0.5	1.0
	Tobramycin	0.5–2.0	1.0	1.0
Enterobacter sp. (25)[a]	A49759	0.5–8.0	2.0	4.0
	Amikacin	0.5–4.0	1.0	4.0
	Fortimicin A	1.0–8.0	2.0	4.0
	Gentamicin	≤0.25–2.0	0.5	1.0
	Netilmicin	≤0.25–0.5	0.5	0.5
	Sisomicin	≤0.25–1.0	0.5	0.5
	Tobramycin	≤0.25–2.0	0.5	1.0
K. pneumoniae (25)	A49759	1.0–4.0	2.0	2.0
	Amikacin	0.5–4.0	1.0	2.0
	Fortmicin A	1.0–8.0	2.0	4.0
	Gentamicin	≤0.25–8.0	≤0.25	1.0
	Netilmicin	≤0.25–1.0	≤0.25	0.5
	Sisomicin	≤0.25–2.0	0.5	1.0
	Tobramycin	≤0.25–16	0.5	1.0
Proteus mirabilis (25)	A49759	0.5–4.0	2.0	2.0
	Amikacin	0.5–16	2.0	8.0
	Fortimicin A	1.0–16	4.0	8.0
	Gentamicin	≤0.25–4.0	1.0	2.0
	Netilmicin	≤0.25–4.0	1.0	2.0
	Sisomicin	≤0.25–2.0	0.5	1.0
	Tobramycin	≤0.25–2.0	0.5	1.0
Proteus spp., indole positive (32)[b]	A49759	0.5–32	2.0	8.0
	Amikacin	0.5–8.0	1.0	2.0
	Fortimicin A	0.5–64	2.0	8.0
	Gentamicin	≤0.25–64	0.5	16
	Netilmicin	≤0.25–64	0.5	16
	Sisomicin	≤0.25–32	0.5	4.0
	Tobramycin	≤0.25–32	1.0	8.0
Providencia stuartii (25)	A49759	≤0.25–>128	1.0	8.0
	Amikacin	≤0.25–>128	1.0	4.0
	Fortimicin A	0.5–>128	2.0	8.0
	Gentamicin	≤0.25–>128	8.0	32
	Netilmicin	≤0.25–>128	8.0	32
	Sisomicin	≤0.25–64	4.0	8.0
	Tobramycin	≤0.25–>128	4.0	16
S. marcescens (25)	A49759	1.0–8.0	2.0	4.0
	Amikacin	1.0–16	2.0	8.0
	Fortimicin A	2.0–8.0	4.0	8.0
	Gentamicin	0.5–64	1.0	16
	Netilmicin	0.5–16	2.0	4.0
	Sisomicin	≤0.25–32	0.5	8.0
	Tobramycin	1.0–>128	4.0	128

[a] Includes *Enterobacter cloacae* (10), *Enterobacter aerogenes* (10), and *Enterobacter agglomerans* (5).
[b] Includes *Morganella morganii* (11), *Proteus vulgaris* (10), and *Providencia rettgeri* (11).

ity mutants. A49759 and fortimicin A are clearly active in vitro against bacterial strains possessing 3′-phosphotransferase [APH(3′)], 4′-nucleotidyltransferase [ANT(4′)], 2″-nucleotidyltransferase [ANT(2″)], AAC(6′), and some AAC(3) enzymes (5). Due to the lower A49759 activity against *P. aeruginosa*, the extent of susceptibility to AAC(3)-I could not be accurately determined. Previous reports using AAC(3)-I-producing *Enterobacteriaceae* revealed significant inactivation of the pseudodisaccharide aminoglycosides (13). All drugs failed to significantly (MICs, ≤16 μg/ml) inhibit enteric or pseudomonad isolates having permeability mutations.

TABLE 2. *MICs inhibiting 50 and 90% of strains and MIC ranges for seven animoglycosides tested against 164 strains of nonfermentative gram-negative bacilli, staphylococci, and streptococci*

Organism (no. of isolates)	Aminoglycoside	MIC range (μg/ml)	MIC 50 (μg/ml)	MIC 90 (μg/ml)
Acinetobacter calcoaceticus var. *anitratus* (14)	A49759	2.0–128	2.0	8.0
	Amikacin	1.0–32	2.0	2.0
	Fortimicin A	2.0–16	4.0	16
	Gentamicin	0.5–1.0	0.5	4.0
	Netilmicin	0.5–>128	2.0	32
	Sisomicin	0.5–128	0.5	4.0
	Tobramycin	0.5–64	0.5	8.0
Pseudomonas sp. (31)	A49759	≤0.25–>128	2.0	>128
	Amikacin	≤0.25–>128	2.0	128
	Fortimicin A	0.5–>128	4.0	>128
	Gentamicin	≤0.25–>128	0.5	>128
	Netilmicin	≤0.25–>128	0.5	>128
	Sisomicin	≤0.25–>128	0.5	128
	Tobramycin	≤0.25–>128	0.5	128
H. influenzae, ampicillin susceptible (19)	A49759	1.0–4.0	2.0	4.0
	Amikacin	2.0–8.0	4.0	8.0
	Fortimicin A	1.0–4.0	4.0	4.0
	Gentamicin	0.5–2.0	1.0	2.0
	Netilmicin	≤0.25–1.0	0.5	1.0
	Sisomicin	≤0.25–1.0	1.0	1.0
	Tobramycin	0.5–2.0	1.0	2.0
H. influenzae, ampicillin resistant (20)	A49759	2.0–4.0	2.0	2.0
	Amikacin	2.0–8.0	2.0	4.0
	Fortimicin	2.0–4.0	2.0	4.0
	Gentamicin	1.0–2.0	1.0	2.0
	Netilmicin	0.5–1.0	0.5	1.0
	Sisomicin	0.5–1.0	0.5	1.0
	Tobramycin	1.0–2.0	1.0	2.0
S. pneumoniae (19)	A49759	8–64	32	64
	Amikacin	8–>64	64	>64
	Fortimicin A	4–64	32	32
	Gentamicin	1.0–32	16	32
	Netilmicin	2.0–16	8.0	16
	Sisomicin	1.0–16	8.0	16
	Tobramycin	8.0–64	16	64
S. pyogenes (20)	A49759	4.0–64	32	32
	Amikacin	8.0–>64	>64	>64
	Fortimicin A	8.0–64	32	64
	Gentamicin	2.0–32	16	32
	Netilmicin	2.0–16	16	16
	Sisomicin	2.0–16	8	16
	Tobramycin	16–64	32	64
S. aureus, methicillin susceptible (50)	A49759	≤0.25–64	≤0.25	1.0
	Amikacin	≤0.25–2.0	1.0	2.0
	Fortimicin A	≤0.25–128	1.0	2.0
	Gentamicin	≤0.25–64	≤0.25	0.5
	Netilmicin	≤0.25–2.0	≤0.25	0.5
	Sisomicin	≤0.25–16	≤0.25	0.5
	Tobramycin	≤0.25–16	≤0.25	0.5
S. aureus, methicillin resistant (10)	A49759	≤0.25–2.0	≤0.25	1.0
	Amikacin	≤0.25–2.0	1.0	2.0
	Fortimicin A	≤0.25–2.0	1.0	2.0
	Gentamicin	≤0.25–0.5	≤0.25	0.5
	Netilmicin	≤0.25–0.5	≤0.25	0.5
	Sisomicin	≤0.25–0.5	≤0.25	0.5
	Tobramycin	≤0.25–8.0	≤0.25	1.0

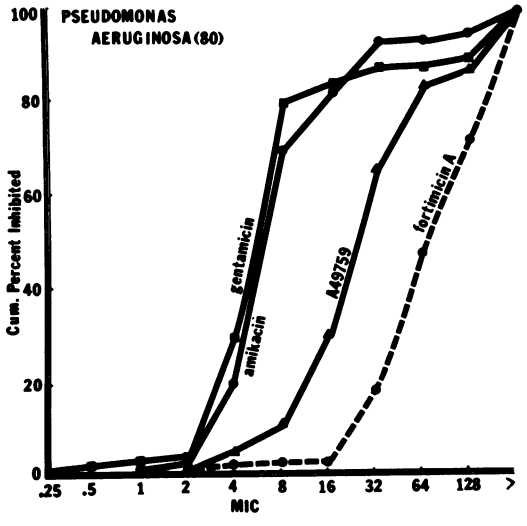

FIG. 1. *Cumulative percentage curves for 80 moderately resistant strains of P. aeruginosa tested against A49759, amikacin, fortimicin A, and gentamicin.*

MIC studies using the same Mueller-Hinton broth lot without divalent cation supplement demonstrated four- to eightfold lower A49759 MIC values against *P. aeruginosa* only. All other aminoglycosides showed similar MIC shifts.

DISCUSSION

Abbott compound A49759, a derivative of fortimicin A, possesses in vitro antimicrobial activity superior to that described previously for fortimicin aminoglycosides (6–8, 10, 14, 15). Its increased activity against *P. aeruginosa* compared with that of fortimicin A also seems superior to those recently described for sannamycin A, sporaricin A, and istamycin B (3, 4, 11). A49759 was very active against the *Enterobacteriaceae*, other pseudomonads, acinetobacters, and the staphylococci. Streptococci, especially *Streptococcus faecalis*, were not significantly inhibited by the tested aminoglycosides.

The pseudodisaccharide aminocyclitols are generally resistant to most bacteria-mediated

TABLE 3. *MLC/MIC ratios of A49759 and six aminoglycoside antimicrobics tested against 70 bacterial isolates from nine genera*

Organism (no. of isolates)	Antibiotic	MLC/MIC ratio		
		1	2	≥4
P. aeruginosa (10)	A49759	4	5	1
	Amikacin	7	2	1
	Fortimicin A	4	2	0
	Gentamicin	7	3	0
	Netilmicin	8	2	0
	Sisomicin	9	1	0
	Tobramycin	10	0	0
S. aureus (10)	A49759	8	2	0
	Amikacin	7	1	2
	Fortimicin A	7	1	2
	Gentamicin	10	0	0
	Netilmicin	10	0	0
	Sisomicin	10	0	0
	Tobramycin	8	2	0
Proteus, Providencia, and *Morganella* spp. (10)	A49759	5	4	1
	Amikacin	4	4	2
	Fortimicin A	7	2	1
	Gentamicin	8	1	1
	Netilmicin	10	0	0
	Sisomicin	7	3	0
	Tobramycin	7	2	1
Other *Enterobacteriaceae* (40)[a]	A49759	30	10	0
	Amikacin	36	4	0
	Fortimicin A	32	7	1
	Gentamicin	37	2	1
	Netilmicin	34	2	4
	Sisomicin	30	8	2
	Tobramycin	35	4	1

[a] Enteric organisms include *E. coli* (10), *Enterobacter cloacae* (5), *Enterobacter aerogenes* (5), *K. pneumoniae* (10), and *S. marcescens* (10).

TABLE 4. *The effect of increasing inoculum concentrations on the MIC 90 values for seven categories of bacteria tested against seven aminoglycosides*

Organism (no. of isolates)	MIC (μg/ml) at inoculum density (log_{10} scale CFU/ml):																				
	A49759			Amikacin			Fortimicin A			Gentamicin			Netilmicin			Sisomicin			Tobramycin		
	3	5	7	3	5	7	3	5	7	3	5	7	3	5	7	3	5	7	3	5	7
E. coli (10)	4	4	32	2	4	32	4	8	64	1	2	16	1	1	16	0.5	1	8	1	2	16
Enterobacter spp. (10)[a]	1	2	8	1	2	8	2	4	8	0.5	0.5	4	0.5	0.5	1	≤0.25	0.5	2	0.5	0.5	4
K. pneumoniae (10)	2	2	16	1	4	16	2	4	32	0.5	2	4	1	1	4	0.5	1	2	1	1	8
Proteus spp. indole positive (20)[b]	1	4	16	1	4	32	8	8	64	2	2	32	2	2	16	1	4	16	2	2	32
S. marcescens (10)	1	4	16	2	2	16	2	2	16	1	1	4	2	4	16	1	1	8	4	8	32
P. aeruginosa (10)	16	32	64	8	32	32	>128	>128	>128	8	16	32	8	32	32	4	16	16	8	16	16
S. aureus (10)	1	2	4	2	4	8	2	4	8	0.5	1	4	0.5	1	2	≤0.25	≤0.25	1	≤0.25	0.5	2

[a] Includes *E. cloacae* (5) and *E. aerogenes* (5).
[b] Includes *Morganella morganii* (4), *P. vulgaris* (2), and *Providencia rettgeri* (4).

TABLE 5. *MICs of A49759 and six aminoglycosides against 10 representative organisms possessing known resistance mechanisms*

Resistance mechanism	Bacterial species	Geometric mean MIC (μg/ml)						
		A49759	Fortimicin A	Amikacin	Gentamicin	Netilmicin	Sisomicin	Tobramycin
APH(3')-I[a]	*E. coli*	4	8	4	2	2	1	4
APH(3')-IV	*S. aureus*	4	8	64	1	1	1	4
ANT(4')	*S. aureus*	1	4	16	1	0.5	0.5	>128
ANT(2'')	*Serratia liquefaciens*	≤0.5	1	4	64	1	16	64
AAC(3)-I	*P. aeruginosa*	32	128	16	>128	>128	>128	4
AAC(3)-II	*S. marcescens*	4	8	8	>128	32	64	16
AAC(3)-III	*E. coli*	1	2	2	64	16	64	16
AAC(6')-I	*E. coli*	4	4	32	2	64	4	32
AAC(6')-II	*P. aeruginosa*	>128	128	32	>128	>128	>128	>128
Perm[b]	*E. coli*	64	128	64	32	64	32	16

[a] See references 5 and 15 for classification of bacterial enzymes.
[b] Permeability mutant.

inactivating enzymes (3, 4, 11, 13–15). Only the AAC(3)-I enzyme (3-*N*-acetylation) routinely inactivates this series of drugs, as well as gentamicin, netilmicin, and sisomicin. Only amikacin and tobramycin among the currently available aminoglycosides were active against these isolates in vitro (3, 5, 12). Conversely, the AAC(6′) enzymes (6′-*N*-acetylation) will not inactivate A49759 or fortimicin A, but they confer resistance against most other aminoglycosides, including amikacin and netilmicin. None of the drugs tested was effective against the cell wall permeability mutants at ≤16 μg/ml.

The divalent cation content of the test broth exerts a profound effect on some A49759 MICs. The MIC increase of four- to eightfold associated with raising cation concentrations was similar to that described for other aminoglycosides tested against *P. aeruginosa* (2, 5; manuscript in preparation). Increasing inoculum also increased A49759 MICs, especially at 10^7 CFU/ml. A49759 had 97% of MLCs within fourfold of the MIC result, a finding comparable to that of gentamicin, sisomicin, and tobramycin.

We conclude that A49759 is a very active new pseudodisaccharide aminoglycoside having inhibitory and killing effects on a wide variety of bacteria. The superiority of A49759 to the related compound fortimicin A and its potential for lower in vivo toxicity support continued in vitro and in vivo investigations.

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