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In Vitro Activity of A-56268 (TE-031), a New Macrolide Antibiotic, Compared with That of Erythromycin and Other Antimicrobial Agents

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A-56268 is a new macrolide antibiotic that resembles erythromycin in its spectrum of activity. A-56268 and erythromycin had identical activities against *Streptococcus pyogenes*, group B, C, and G streptococci, and viridans group streptococci. Erythromycin and A-56268 had similar activities against *Staphylococcus aureus*, coagulase-negative staphylococci, and group D enterococci. Like erythromycin, A-56268 was ineffective in inhibiting oxacillin-resistant *S. aureus*, oxacillin-resistant, coagulase-negative staphylococci, and penicillin-resistant viridans group streptococci. *Haemophilus influenzae*, *Neisseria gonorrhoeae*, and *Legionella* spp. were inhibited by A-56268 at concentrations similar to those of erythromycin.

Macrolide antibiotics are relatively nontoxic and are frequently used for the treatment of infections caused by susceptible gram-positive bacteria. Erythromycin has been the most widely used, principally as an alternative to penicillin in penicillin-allergic patients. Erythromycin has retained excellent activity against most of the common streptococcal species, including *Streptococcus pneumoniae*. It has been the primary therapeutic agent for *Mycoplasma pneumoniae* and *Legionella* infections. However, erythromycin produces gastrointestinal discomfort in some patients, and its pharmacokinetics are not completely satisfactory, owing to its instability in gastric juices. A-56268 is a new macrolide antibiotic which may offer significant advantages over erythromycin as far as tolerance and pharmacokinetics are concerned. To evaluate the overall in vitro activity of this agent, we performed MIC determinations for 259 clinical isolates. The activity of A-56268 was compared with those of erythromycin and other conventional compounds against 204 commonly encountered gram-positive isolates, 39 gram-negative organisms, and 16 *Legionella* isolates.

A-56268 was a gift from Abbott Laboratories, North Chicago, Ill., as was erythromycin. Vancomycin was provided by Eli Lilly & Co., Indianapolis, Ind., and clindamycin was provided by The Upjohn Co., Kalamazoo, Mich. Penicillin was obtained from Wyeth Laboratories, Philadelphia, Pa. All compounds were prepared in accordance with manufacturer instructions. Isolates tested were obtained from patients at the University of California at Los Angeles Medical Center, with the exception of the *Legionella* isolates. These were obtained from Paul Edelstein of the Veterans Administration Wadsworth Medical Center, Los Angeles, Calif.

MICs for nonfastidious organisms were determined by microdilution as described by the National Committee for Clinical Laboratory Standards (4). Mueller-Hinton broth supplemented with 50 mg of Ca^{2+} and 25 mg of Mg^{2+} per liter was used. MIC trays were inoculated by the direct inoculum method to obtain a final concentration of 10^5 CFU/ml. After 16 to 18 h of incubation at 35°C, MIC endpoints were read manually. National Committee for Clinical Laboratory Standards protocol (4) was likewise followed in determining standard agar dilution MICs for nonenterococcal streptococci. Approximately 10^4 CFU were delivered to Mueller-Hinton agar supplemented with 5% sheep blood. The MIC was defined as the lowest concentration of antimicrobial agent which allowed the growth of no more than one colony. Following the suggested modifications in National Committee for Clinical Laboratory Standards M7-A (4), we tested *Haemophilus influenzae* by macrobroth dilution with Mueller-Hinton broth supplemented with 50 mg of Ca^{2+} and 25 mg of Mg^{2+} per liter, 3% lysed horse blood, and NAD (10 μg/ml). *Neisseria gonorrhoeae* was tested by agar dilution on GC agar base (Difco Laboratories, Detroit, Mich.) supplemented with 1% IsoVitaleX (BBL Microbiology Systems, Cockeysville, Md.) and incubated at 35°C in an atmosphere of 5% CO_2 for 24 h. Agar dilution was used to determine MICs for *Legionella* spp. as described by Edelstein et al. (2). Approximately 10^5 CFU were delivered to buffered charcoal-yeast extract agar (Remel, Lenexa, Kans.) and incubated at 35°C in 5% CO_2 for 48 h.

The overall activity of A-56268 is shown in Table 1. A-56268 was very active against *Corynebacterium* spp. and *Listeria monocytogenes* (MICs for 90% of strains [MIC_{90}s], 0.25 and 0.12 μg/ml, respectively). This activity was similar to that of erythromycin against *Corynebacterium* spp. but greater than that of erythromycin against *L. monocytogenes*. Against oxacillin-susceptible *Staphylococcus aureus* and coagulase-negative staphylococci, A-56268 and erythromycin had equivalent MICs for 50% of strains (MIC_{50}s) and MIC_{90}s (0.25 and >32 μg/ml, respectively). Neither oxacillin-resistant *S. aureus* nor oxacillin-resistant coagulase-negative staphylococci were inhibited by 32 μg of A-56268 or erythromycin per ml. *Streptococcus faecalis* isolates susceptible or moderately susceptible to erythromycin were also susceptible to A-56268 (MIC_{90}, 1.0 μg/ml), and those resistant to erythromycin were resistant to A-56268. A-56268 had in vitro efficacy identical to those of erythromycin and penicillin against beta-hemolytic group A and B streptococci (MIC_{90}, 0.12 μg/ml) and had moderate activity against those

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TABLE 1. Comparative activities of A-56268 and other antimicrobial compounds

Organism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)		
		Range	50%	90%
Corynebacterium spp. (12)	A-56268	0.03–0.25	0.12	0.25
	Erythromycin	0.03–0.5	0.25	0.5
	Clindamycin	0.25–8	2	>8
	Vancomycin	0.4–0.8	0.8	0.8
Listeria monocytogenes (10)	A-56268	0.06–0.12	0.12	0.12
	Erythromycin	0.12–0.5	0.25	0.5
	Clindamycin	0.5–1	1	1
	Vancomycin	0.8–1.6	0.8	1.6
Staphylococcus aureus (29) (oxacillin susceptible)	A-56268	0.12–>32	0.25	>32
	Erythromycin	0.5–>32	0.5	>32
	Clindamycin	0.12–>8	0.25	>8
	Vancomycin	0.4–3.2	0.8	1.6
Staphylococcus aureus (29) (oxacillin resistant)[a]	A-56268	>32	>32	>32
	Erythromycin	>32	>32	>32
	Clindamycin	>8	>8	>8
	Vancomycin	0.8–3.2	1.6	3.2
Coagulase-negative staphylococci (37) (oxacillin susceptible)	A-56268	0.06–>32	0.25	>32
	Erythromycin	0.12–>32	0.25	>32
	Clindamycin	0.12–0.25	0.12	0.25
	Vancomycin	0.8–3.2	1.6	3.2
Coagulase-negative staphylococci (12) (oxacillin resistant)	A-56268	>32	>32	>32
	Erythromycin	>32	>32	>32
	Clindamycin	>8	>8	>8
	Vancomycin	1.6–3.2	1.6	3.2
Streptococcus faecalis (20) (erythromycin susceptible)	A-56268	0.12–1	0.5	1
	Erythromycin	0.25–2	1	2
	Vancomycin	0.8–3.2	3.2	3.2
Streptococcus faecalis (9) (erythromycin resistant)[b]	A-56268	8.0–>32		>32
	Erythromycin	8.0–>32		>32
	Vancomycin	0.8–3.2		3.2
Streptococcus pyogenes (8)	A-56268	0.03–0.12		0.12
	Erythromycin	0.06–0.12		0.12
	Clindamycin	0.06–0.12		0.12
	Penicillin	≤0.03–0.12		0.12
Streptococcus spp. group B (11)	A-56268	0.12	0.12	0.12
	Erythromycin	0.12	0.12	0.12
	Clindamycin	0.06–0.12	0.12	0.12
	Penicillin	0.06–0.12	0.06	0.12
Streptococcus spp. group C (8)	A-56268	0.06–0.25		0.25
	Erythromycin	0.03–0.25		0.25
	Clindamycin	0.03–0.5		0.5
	Penicillin	0.03–0.06		0.06
Streptococcus spp. group G (8)	A-56268	0.06–0.25		0.25
	Erythromycin	0.12		0.12
	Clindamycin	0.12–0.25		0.25
	Penicillin	0.03–0.06		0.06
Viridans group streptococci (10) (penicillin susceptible)	A-56268	0.06–4	0.06	0.12
	Erythromycin	0.03–4	0.06	0.12
Viridans group streptococci (10) (penicillin resistant)[c]	A-56268	0.03–4	0.12	4
	Erythromycin	0.06–4	0.12	4
Legionella pneumophila (9)	A-56268	0.06–1		0.25
	Erythromycin	0.12–1	0.5	
Legionella spp. (7)[d]	A-56268	0.12–0.5		0.5
	Erythromycin	0.25–0.5		0.5

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TABLE 1. —*Continued*

Organism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)		
		Range	50%	90%
Neisseria gonorrhoeae (20)	A-56268	≤0.03–1	0.25	1
	Erythromycin	≤0.06–1	0.5	1
Haemophilus influenzae (19)	A-56268	0.12–4	1	2
	Erythromycin	0.25–2	2	2

[a] MIC, >2 μg/ml.
[b] MIC, >4 μg/ml.
[c] Includes those organisms demonstrating increased resistance to penicillin (MIC, ≥0.25 μg/ml).
[d] Includes *L. wadsworthii*, *L. micdadei*, and *L. longbeachae*.

isolates with penicillin MICs of 0.25 to 2.0 μg/ml (MIC_{50} and MIC_{90}, 0.12 and 4.0 μg/ml, respectively). The activities of A-56268 and erythromycin for *N. gonorrhoeae* were similar (MIC_{90}s, 1.0 and 2.0 μg/ml, respectively). *H. influenzae* isolates (90%) were inhibited by ≤2.0 μg of both A-56268 and erythromycin per ml. All *Legionella* spp. tested were susceptible to A-56268 (MIC_{90}, 0.5 μg/ml), which had activity equivalent to that of erythromycin.

The spectrum of activity of A-56268, a new macrolide antibiotic, compared favorably with that of erythromycin against the bacterial isolates in this study. Like erythromycin, A-56268 had MICs of ≤0.5 μg/ml against a majority of gram-positive isolates. The activity of A-56268 against *Legionella* spp. was comparable to that of erythromycin, and its in vitro efficacy against *N. gonorrhoeae* and *H. influenzae* was similar or equal to that of erythromycin. These results are comparable to those reported for other experimental macrolides (1–3). A-56268 appears to be a promising new macrolide that has antimicrobial activity similar to that of erythromycin. Preliminary reports (K. Synder, personal communication) suggest that A-56268 has favorable pharmacological properties and may be better tolerated than erythromycin. In view of these features, further studies on A-56268 to assess its clinical utility seem indicated.

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