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In Vitro Evaluation of S-25930 and S-25932, Two New Quinolones, against Aerobic Gram-Negative Isolates from Cancer Patients

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The in vitro activity of S-25930 and S-25932, two new 4-quinolones, against 450 aerobic gram-negative organisms isolated from cancer patients was evaluated and compared with the activity of ciprofloxacin, enoxacin, difloxacin (A-56619), and A-56620. Both agents inhibited most members of the family *Enterobacteriaceae* at concentrations of ≤2.0 μg/ml, but their activity against *Pseudomonas aeruginosa* was inferior to that of other quinolones. Although considerably less active than ciprofloxacin and A-56620, S-25930 was frequently two- to eightfold more active than S-25932 and was comparable to difloxacin and enoxacin against most isolates.

Aerobic gram-negative organisms account for 70 to 85% of bacterial infections in neutropenic cancer patients (1). Although *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* are isolated most often, other gram-negative bacteria, such as *Acinetobacter* spp., *Aeromonas hydrophila*, and *Pseudomonas* spp. other than *P. aeruginosa*, are being recovered with increasing frequency from this group of patients (3, 6). S-25930 (6,7-dihydro-5,8-dimethyl-9-fluoro-1-oxo-1*H*,5*H*-benzo-[ij]-quinolizine-2-carboxylic acid) and S-25932 (6,7-dihydro-9-fluoro-8-imidazolyl-5-methyl-1-oxo-1*H*,5*H*-benzo-[ij]quinolizine-2-carboxylic acid) are two newly developed 4-quinolone agents with a broad antibacterial spectrum (D. Felmingham, M. D. O'Hare, M. J. Robbins, G. L. Ridgway, and R. N. Grüneberg, Program Abstr. 25th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 138, 1985; H. C. Neu, P. Labthavikul, G. Saha, and N. X. Chin, 25th ICAAC, abstr. no. 139, 1985; L. J. V. Piddock, R. Wise, and J. M. Andrews, 25th ICAAC, abstr. no. 140, 1985). We determined the in vitro activity of these two agents against 450 aerobic gram-negative isolates obtained from blood culture specimens (duplicate isolates from patients with multiple positive blood cultures were excluded) of cancer patients admitted to the University of Texas M. D. Anderson Hospital and Tumor Institute to evaluate their usefulness for the treatment of infections in our patient population. Their activity was also compared with that of four other quinolones.

(This work was presented in part at the 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La., 28 September to 1 October 1986 [K. Rolston, D. Ho, B. LeBlanc, and G. P. Bodey, 26th ICAAC, abstr. no. 355, 1986].)

Laboratory reference standard antimicrobial agents were obtained from their manufacturers as follows: S-25930 and S-25932, Riker Laboratories, St. Paul, Minn.; difloxacin (A-56619) and A-56620, Abbott Laboratories, North Chicago, Ill.; ciprofloxacin, Miles Pharmaceuticals, West Haven, Conn.; enoxacin, Warner-Lambert Pharmaceutical Research, Ann Arbor, Mich. Microtiter broth dilution susceptibility tests were performed by a previously described technique and in accordance with the guidelines set by the National Committee for Clinical Laboratory Standards (4, 5). The test medium was Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) supplemented with Mg^{2+} (25 mg/liter) and Ca^{2+} (50 mg/liter). Antimicrobial concentrations were prepared manually with serial twofold dilutions ranging from 64 to 0.03 μg/ml and dispensed automatically with an MIC-2000 apparatus (Dynatech Laboratories, Inc., Alexandria, Va.) into microtiter plates containing 96 wells (0.1 ml per well). Organisms were inoculated into broth cultures, and appropriate dilutions were made after 18 h of incubation so that the final inoculum tested was approximately 10^5 CFU/ml. The MICs were recorded after 16 to 18 h of incubation at 35°C in ambient air and defined as the lowest concentration of each drug inhibiting visible bacterial growth. *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were included as controls for each procedure.

The data accumulated with the 450 bacterial isolates tested are shown in Table 1. Ciprofloxacin was overall the most active quinolone tested; however, for 9 of the 17 species tested, either A-56620 or difloxacin had similar MICs for 50% of isolates (MIC_{50}s) and MIC_{90}s. A-56620, like ciprofloxacin, was highly active against *A. hydrophila*, *Citrobacter* spp., *E. coli*, *Enterobacter* spp., and *Klebsiella* spp. Both these agents were active against *P. aeruginosa*, although ciprofloxacin was far more so. S-25930 was active against *Acinetobacter* spp. and *A. hydrophila*, inhibiting all isolates at a concentration of ≤0.5 μg/ml. It also inhibited most members of the family *Enterobacteriaceae* at ≤0.5 μg/ml, with the exception of *Citrobacter freundii* (MIC_{90}, 2.0 μg/ml) and *Enterobacter aerogenes* and *K. pneumoniae* (MIC_{90}, 1.0 μg/ml for each). S-25932 was frequently two- to eightfold less active than S-25930. The antibacterial spectrum of both agents was limited by relatively poor activity against *P. aeruginosa* and *Pseudomonas maltophilia*.

Interest in the quinolones has been rekindled in the past several years by the introduction of several new agents with a broad antibacterial spectrum and great in vitro potency (2). The two new agents evaluated in this study, S-25930 and S-25932, were less active in vitro than agents such as ciprofloxacin and A-56620 against most gram-negative aerobes. They could, however, still be clinically useful compounds if superior pharmacokinetic properties resulting in enhanced levels in blood and tissues can be demonstrated or if they are less toxic than other quinolones. Their usefulness might be limited by relatively poor activity against *P. aeruginosa*, a frequent pathogen in neutropenic patients.

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TABLE 1. In vitro activity of six quinolone agents against 450 bacterial isolates representing 17 species

Species (no. of isolates tested)	MIC (μg/ml)											
	S-25930		S-25932		Ciprofloxacin		Enoxacin		Difloxacin		A-56620	
	50%	90%	50%	90%	50%	90%	50%	90%	50%	90%	50%	90%
Acinetobacter calcoaceticus subsp. *anitratus* (25)	0.25	0.5	2.0	4.0	0.125	0.25	1.0	2.0	0.06	0.125	0.06	0.25
A. calcoaceticus subsp. *lwoffi* (25)	0.125	0.25	2.0	4.0	0.06	0.125	0.5	1.0	0.03	0.125	0.06	0.125
Aeromonas hydrophila (15)	≤0.03	0.5	0.25	1.0	≤0.03	0.06	≤0.03	0.25	0.06	0.25	≤0.03	0.06
Citrobacter diversus (20)	0.25	0.5	0.25	0.5	≤0.03	≤0.03	0.06	0.125	0.06	0.25	≤0.03	0.03
Citrobacter freundii (20)	0.25	2.0	0.25	4.0	≤0.03	≤0.03	0.125	0.5	0.125	1.0	≤0.03	0.125
Enterobacter aerogenes (20)	0.5	1.0	0.5	1.0	≤0.03	≤0.03	0.125	0.125	0.125	0.25	≤0.03	0.03
E. agglomerans (15)	0.25	0.5	0.5	2.0	≤0.03	≤0.03	0.125	0.5	0.06	0.25	≤0.03	0.06
E. cloacae (30)	0.5	0.5	0.5	1.0	≤0.03	≤0.03	0.125	0.25	0.125	0.25	≤0.03	0.03
Escherichia coli (50)	0.125	0.25	0.25	0.25	≤0.03	≤0.03	0.06	0.125	0.06	0.125	≤0.03	0.03
Klebsiella oxytoca (25)	0.25	0.5	0.25	0.5	≤0.03	≤0.03	0.125	0.25	0.125	0.25	≤0.03	≤0.03
K. pneumoniae (50)	0.25	1.0	0.5	2.0	≤0.03	0.06	0.125	1.0	0.25	1.0	0.03	0.25
Morganella morganii (15)	0.25	0.25	0.5	1.0	≤0.03	≤0.03	0.125	0.125	0.125	0.5	0.03	0.125
Proteus mirabilis (30)	0.5	0.5	1.0	1.0	≤0.03	≤0.03	0.25	0.5	1.0	1.0	0.125	0.25
P. vulgaris (15)	0.125	0.25	1.0	1.0	≤0.03	≤0.03	0.125	0.25	0.5	1.0	0.06	0.125
Pseudomonas aeruginosa (50)	4.0	16.0	8.0	32.0	0.06	0.25	0.5	2.0	2.0	8.0	1.0	2.0
P. maltophilia (15)	4.0	8.0	16.0	32.0	2.0	8.0	8.0	16.0	1.0	8.0	1.0	2.0
Serratia marcescens (30)	1.0	1.0	2.0	2.0	≤0.03	0.06	0.25	0.5	1.0	2.0	0.125	0.25

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