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In Vitro Activity of Win 49375 Compared with Those of Other Antibiotics in Isolates from Cancer Patients

IBRAHIM GARCIA,* GERALD P. BODEY, VICTOR FAINSTEIN, DAH HSI HO, AND BARBARA LEBLANC

Section of Infectious Diseases, Department of Internal Medicine, The University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77030

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The activity of WIN 49375 [6-fluoro-1,4-dihydro-1-(methylamino)-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid], a new synthetic quinolone, was tested in vitro against 587 clinical isolates. The MICs for 90% of isolates of *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* were 0.20, 1.56, and 0.39 μg/ml, respectively. The MICs for 90% of isolates of *Pseudomonas aeruginosa* and *Serratia marcescens* were both 3.12 μg/ml. WIN 49375 was minimally active against gram-positive cocci. Its in vitro activity suggests that it may be useful for the treatment of gram-negative bacillary infections.

WIN 49375 [6-fluoro-1,4-dihydro-1-(methylamino)-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid] is a new synthetic antibacterial agent of the fluoroquinolone class. It is active against most aerobic gram-negative bacteria, including *Pseudomonas aeruginosa*, an important cause of morbidity and mortality in cancer patients (1). WIN 49375 has been proven to be efficacious in bacterial infections under experimental conditions in neutropenic rats when administered by oral or parenteral routes (R. A., Dobson, R. B. Wagner, and J. B. Cornett, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 23rd, Las Vegas, Nev., abstr. no. 705, 1983). Because of its activity against many organisms which commonly cause infection in cancer patients, we have conducted an in vitro evaluation of WIN 49375 against 587 clinical isolates obtained at our institution.

A total of 475 clinical isolates of gram-negative bacilli and 112 isolates of gram-positive cocci were tested. All gram-negative bacilli were isolated from blood cultures obtained from cancer patients at this institution during the past 10 years. Isolates of gram-positive cocci were obtained from cultures taken from various body sites of hospitalized patients, some of whom did not have cancer. All isolates were maintained in stock by lyophilization or ultrafreezing methods. Organisms were tested in duplicate simultaneously. The *Staphylococcus aureus* isolates were selected on the basis of an MIC of ≤0.01 μg/ml (penicillin G susceptible) or ≥25 μg/ml (penicillin G resistant). Appropriate dilutions were made so that the final concentration of organisms was 10^5 CFU/ml (10^6 CFU/ml for *Streptococcus pyogenes* and *Streptococcus pneumoniae*). The concentration and purity of all isolates were confirmed by plate counting.

WIN 49375 was supplied by Sterling-Winthrop Research Institute, Rensselaer, N.Y.; moxalactam and tobramycin were supplied by Eli Lilly & Co., Indianapolis, Ind.; imipenem was supplied by Merck & Co., Inc., Rahway, N.J.; ceftazidime was supplied by Glaxo Research Ltd., Ft. Lauderdale, Fla.; mezlocillin was supplied by Miles Laboratories, Inc., Westhaven, Conn.; aztreonam was supplied by E. R. Squibb & Sons, Inc., Princeton, N.J.; and piperacillin was supplied by Lederle Laboratories, Pearl River, N.Y.

Serial antibiotic concentrations were prepared in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) for all organisms except *Streptococcus pyogenes* and *Streptococcus pneumoniae*, for which tryptose phosphate broth (Difco) was used. Antibiotic solutions were dispensed automatically by a Dynatech MIC-2000 Dispenser (Dynatech Laboratories, Inc., Alexandria, Va.) for susceptibility testing.

In performing susceptibility testing with isolates of *Streptococcus pyogenes* and *Streptococcus pneumoniae*, the microtiter plates were inoculated manually. A 0.05-ml sample of a 1:100 dilution of broth cultures of *Streptococcus pyogenes* and *Streptococcus pneumoniae* incubated in a 5% CO_2 incubator at 37°C for 18 h was dripped by a calibrated pipette dropper into wells containing 0.05 ml of various antibiotic concentrations to achieve a final inoculum concentration of ca. 10^6 CFU/ml.

The MIC was defined as the lowest concentration of drug that suppressed visible growth after incubation at 37°C for 18 h for gram-negative bacilli, *S. aureus*, and enterococci. *Streptococcus pyogenes* and *Streptococcus pneumoniae* were incubated at 37°C in CO_2 for 24 h. *S. aureus* ATCC 25923, *Escherichia coli* ATCC 25922, and *P. aeruginosa* ATCC 27853 were included as controls during each procedure.

The in vitro activity of WIN 49375 is summarized in Table 1. The MICs for 90% of isolates of all gram-negative bacilli tested, except *P. maltophilia*, were ≤3.12 μg/ml. This concentration inhibited 100% of the isolates of *E. coli*, *Citrobacter diversus*, and *Enterobacter cloacae*. A concentration of 12.5 μg/ml inhibited 100% of the isolates of *P. aeruginosa*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Proteus mirabilis*, and *Acinetobacter* spp. The MIC of this drug for 90% of isolates of penicillin G-susceptible and penicillin G-resistant *S. aureus* strains was 1.56 μg/ml. This drug was not active against *Streptococcus pyogenes*, enterococci, or *Streptococcus pneumoniae*.

The activity of WIN 49375 against gram-negative bacilli was compared with the activities of moxalactam, ceftazidime, aztreonam, imipenem, piperacillin, mezlocillin, and tobramycin (Table 1). WIN 49375 was the most active drug against *E. coli*, *P. maltophilia*, and *Enterobacter cloacae*. All of these compounds showed poorer activity against *P. maltophilia* than against other gram-negative bacilli. WIN 49375 was as active as ceftazidime and imipenem against *P. aeruginosa* but less active than tobramycin. Against *Serratia marcescens*, ceftazidime and aztreonam showed better activity than WIN 49375. WIN 49375 was more active than tobramycin and moxalactam against *Acinetobacter* and *Citrobacter* spp. However, imipenem was the most active antibiotic against these organisms.

* Corresponding author.

TABLE 1. Comparative in vitro activities of antibiotics against microorganisms

Organisms (no. of isolates tested)	Drug	MIC (μg/ml)[a]		
		Range	50%	90%
Gram-negative organisms				
Enterobacter cloacae (61)	WIN 49375	≤0.05–3.12	0.10	0.39
	Moxalactam	≤0.10–100	0.78	12.5
	Ceftazidime	≤0.10–>100	1.56	100
	Aztreonam	≤0.10–>100	0.78	100
	Imipenem	≤0.012–6.25	0.78	3.12
	Piperacillin	0.20–>100	12.5	>100
	Mezlocillin	0.20–>100	12.5	>100
	Tobramycin	≤0.05–50	0.78	6.25
Escherichia coli (64)	WIN 49375	≤0.05–1.56	≤0.05	0.20
	Moxalactam	≤0.10–12.5	0.20	0.39
	Ceftazidime	≤0.10–>100	0.20	0.39
	Aztreonam	≤0.10–>100	0.10	0.39
	Imipenem	0.50–3.12	0.20	0.39
	Piperacillin	0.39–>100	1.56	>100
	Mezlocillin	0.78–>100	3.12	>100
	Tobramycin	0.20–25	1.56	3.12
Klebsiella pneumoniae (59)	WIN 49375	0.05–12.5	0.10	1.56
	Moxalactam	0.10–25	0.20	1.56
	Ceftazidime	0.10–25	0.20	0.78
	Aztreonam	0.10–>100	0.10	0.39
	Imipenem	0.10–6.25	0.39	1.56
	Piperacillin	0.78–>100	6.25	<100
	Mezlocillin	0.39–>100	12.5	<100
	Tobramycin	0.10–>50	0.78	12.5
Pseudomonas aeruginosa (63)	WIN 49375	0.39–6.25	0.78	3.12
	Moxalactam	3.12–>100	25	>100
	Ceftazidime	0.78–>100	1.56	50
	Aztreonam	0.78–>100	6.25	100
	Imipenem	0.39–>25	1.56	3.12
	Piperacillin	1.56–>100	6.25	100
	Mezlocillin	3.12–>100	25	>100
	Tobramycin	0.10–50	0.20	0.39
Proteus mirabilis (60)	WIN 49375	0.10–12.5	0.20	0.39
	Moxalactam	≤0.10–100	0.20	1.56
	Ceftazidime	≤0.10–>100	0.10	1.56
	Aztreonam	≤0.10–>100	0.10	0.39
	Imipenem	0.20–>25	3.12	6.25
	Piperacillin	≤0.10–100	0.39	0.78
	Mezlocillin	0.20–>100	0.78	1.56
	Tobramycin	0.20–6.25	1.56	3.12
Acinetobacter lwoffi (32)	WIN 49375	0.20–12.5	0.39	3.12
	Moxalactam	0.20–100	25	100
	Ceftazidime	0.39–25	1.56	6.25
	Aztreonam	0.10–>100	12.5	100
	Imipenem	0.025–3.12	0.05	0.20
	Piperacillin	1.56–>100	6.25	50
	Mezlocillin	3.12–>100	12.5	50
	Tobramycin	0.05–>50	0.20	3.12
Acinetobacter calcoaceticus var. *anitratus* (32)	WIN 49375	0.20–6.25	0.78	1.56
	Moxalactam	6.25–>100	50	100
	Ceftazidime	1.56–>100	6.25	12.5
	Aztreonam	6.25–>100	50	>100
	Imipenem	0.025–0.78	0.20	0.39
	Piperacillin	0.78–>100	12.5	50
	Mezlocillin	0.39–>100	25	100
	Tobramycin	≤0.05–25	0.78	3.12
Citrobacter freundii (25)	WIN 49375	≤0.05–25	0.10	0.39
	Moxalactam	≤0.10–>100	0.20	12.5
	Ceftazidime	≤0.10–>100	0.39	>100

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TABLE 1—*Continued*

Organisms (no. of isolates tested)	Drug	MIC (μg/ml)[a]		
		Range	50%	90%
	Aztreonam	0.20–>100	0.20	100
	Imipenem	0.20–25	0.78	1.56
	Piperacillin	1.56–>100	12.5	>100
	Mezlocillin	1.56–>100	6.25	100
	Tobramycin	0.20–>50	0.39	25
Citrobacter diversus (15)	WIN 49375	3.12–3.12	3.12	3.12
	Moxalactam	≤0.10–50	0.39	6.25
	Ceftazidime	≤0.10–100	1.56	50
	Aztreonam	≤0.10–>100	0.39	100
	Imipenem	0.10–1.56	0.20	0.78
	Piperacillin	1.56–>100	12.5	>100
	Mezlocillin	1.56–>100	12.5	>100
	Tobramycin	0.39–50	1.56	3.12
Serratia marcescens (44)	WIN 49375	0.10–12.5	0.78	3.12
	Moxalactam	0.20–25	0.78	3.12
	Ceftazidime	≤0.10–12.5	0.20	0.78
	Aztreonam	≤0.10–12.5	0.20	0.78
	Imipenem	0.20–3.12	0.78	1.56
	Piperacillin	0.78–>100	3.12	50
	Mezlocillin	0.78–50	3.12	12.5
	Tobramycin	0.39–50	6.25	25
Pseudomonas maltophilia (20)	WIN 49375	0.78–>50	3.12	12.5
	Moxalactam	1.56–>100	6.25	50
	Ceftazidime	1.56–>100	25	50
	Aztreonam	6.25–>100	>100	>100
	Imipenem	0.78–>25	>25	>25
	Piperacillin	3.12–>100	50	>100
	Mezlocillin	6.25–>100	100	>100
	Tobramycin	0.39–>50	50	>50
Gram-positive organisms[b]				
S. aureus pen G-susceptible (24)		0.39–6.25	0.78	1.56
S. aureus pen G-resistant (25)		0.39–6.25	0.78	1.56
Streptococcus pyogenes (25)		6.25–>50	25	50
Streptococcus pneumoniae (13)		12.5–>50	25	50
Enterococcus (25)		1.56–50	6.25	25

[a] 50% and 90%, MIC required to inhibit 50 and 90% of strains, respectively.
[b] Activity of WIN 49375.

In this study, WIN 49375 had a broad spectrum of activity against most aerobic gram-negative bacteria, including *P. aeruginosa*. WIN 49375 appears to be as active as other quinolone antimicrobial agents, such as enoxacin, norfloxacin, and ciprofloxacin, although these drugs were not tested in this study (2–5). WIN 49375 inhibited 90% of the isolates of penicillin G-susceptible and -resistant *S. aureus* strains tested at concentrations of 1.56 μg/ml. This new agent deserves further evaluation and may prove useful for therapy of infection caused by susceptible organisms.

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