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Comparative In Vitro Activities of Ciprofloxacin, Gemifloxacin, Grepafloxacin, Moxifloxacin, Ofloxacin, Sparfloxacin, Trovafloxacin, and Other Antimicrobial Agents against Bloodstream Isolates of Gram-Positive Cocci

DWIGHT HARDY,[1] DANIEL AMSTERDAM,[2] LIONEL A. MANDELL,[3] AND COLEMAN ROTSTEIN[3]*

Department of Microbiology and Immunology, University of Rochester, Rochester,[1] and Department of Microbiology, Medicine, and Pathology, School of Medicine, University at Buffalo, and Erie County Medical Center, Buffalo,[2] New York, and Division of Infectious Diseases, McMaster University, Henderson Site, Hamilton Health Sciences Corporation, Hamilton, Ontario, Canada[3]

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The in vitro activity of gemifloxacin against 316 bloodstream isolates of staphylococci, pneumococci, and enterococci was compared with the activities of six fluoroquinolones and three other antimicrobial agents. Of the antimicrobial agents tested, gemifloxacin was the most potent against penicillin-intermediate and -resistant pneumococci, methicillin-susceptible and -resistant *Staphylococcus epidermidis* isolates, and coagulase-negative staphylococci.

Due to the increasing penicillin resistance among community-acquired *Streptococcus pneumoniae* isolates (3, 5), as well as the increasing resistance of staphylococci and enterococci to both beta lactams (2, 7) and glycopeptides (6, 10), physicians have sought to establish the efficacy of other antimicrobial agents against these problem pathogens. Newly developed fluoroquinolones such as trovafloxacin, moxifloxacin, and gemifloxacin are potential candidates for the treatment of penicillin-resistant *S. pneumoniae* infections (1) and may also have utility in the treatment of certain staphylococcal and enterococcal infections.

Gemifloxacin, (*R*,*S*)-7-(3-aminomethyl-4-syn-methoxyimino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid methanesulfonate, exhibits broad-spectrum antibacterial activity (4). Among the fluoroquinolones, gemifloxacin putatively has enhanced activity against staphylococci, streptococci, and enterococci (4). Therefore, we compared the in vitro activity of gemifloxacin against 316 bacteremic isolates of gram-positive cocci with those of ciprofloxacin, grepafloxacin, moxifloxacin, ofloxacin, sparfloxacin, and trovafloxacin in addition to three other respiratation-directed antimicrobial agents (amoxicillin-clavulanic acid, cefuroxime, and azithromycin).

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All isolates were obtained from blood cultures of patients at one of three teaching hospitals: Erie County Medical Center, Buffalo, N.Y.; the Henderson Site of Hamilton Health Sciences Corp., Hamilton, Ontario, Canada; or Strong Memorial Hospital, Rochester, N.Y. The microorganisms were detected by BACTEC instrumentation (Becton Dickinson Diagnostic Instrument Systems, Sparks, Md.) at the Henderson and Erie County Medical Center sites and by BacT/Alert (Organon-Teknika, Durham, N.C.) at the Strong Memorial Hospital site. After initial recovery on 5% sheep blood agar, the isolates were preliminarily identified in the participating hospitals' clinical laboratories. Subcultures of the isolates were then transported to the clinical microbiology laboratory of Strong Memorial Hospital for final identification and susceptibility testing. The identity of purported *Staphylococcus aureus* isolates was confirmed by the tube coagulase test, using rabbit plasma. Coagulase-negative staphylococci were identified to the species level by the use of the Staph-Ident system (Analytab Products, Plainview, N.Y.). *S. pneumoniae* strains were characterized by bile solubility and optochin susceptibility. Enterococci were identified by the hydrolysis of esculin in the presence of bile and by growth in 6.5% sodium chloride. All enterococcal isolates were identified as *Enterococcus faecalis* or *Enterococcus faecium* according to results of biochemical profiles obtained by using the Vitek GPI Identification Card (bioMerieux Vitek Inc., Hazelwood, Mo.) or an API 20 Strep strip (bioMerieux Vitek Inc.).

Antimicrobial agent reference powders used in these studies were as follows: amoxicillin-clavulanic acid (SmithKline Beecham Pharmaceuticals, Collegeville, Pa.), cefuroxime (Glaxo-Wellcome, Research Triangle, N.C.), azithromycin (Pfizer Inc., Groton, Conn.), ciprofloxacin (Bayer Inc., West Haven, Conn.), ofloxacin (R. W. Johnson Pharmaceutical Research Institute, Raritan, N.J.), grepafloxacin (Glaxo-Wellcome), sparfloxacin (Rhone-Poulenc Rorer, Collegeville, Pa.), gemifloxacin (Smith Kline Beecham Pharmaceuticals, Harlow, Essex, United Kingdom), moxifloxacin (Bayer Inc.), and trovafloxacin (Pfizer Inc.).

Broth microdilution antimicrobial susceptibility testing was performed in accordance with the National Committee for Clinical Laboratory Standards methodology (8). The reagent powders were dissolved in accordance with the manufacturers' instructions, diluted with Mueller-Hinton broth, and distributed to the wells of microdilution trays. Each tray was inoculated with $\sim 5 \times 10^5$ CFU per well to yield a final volume of 0.1 ml per well. The trays were incubated at 35°C for 24 h. Susceptibility testing for staphylococcal and enterococcal isolates was performed in cation-adjusted Mueller-Hinton broth. Cation-adjusted Mueller-Hinton broth with 3 to 5% lysed horse blood was employed for the susceptibility testing of pneumo-

* Corresponding author. Mailing address: McMaster Medical Unit, Henderson Site, Hamilton Health Sciences Corp., 711 Concession St., Hamilton, Ontario L8V 1C3, Canada. Phone: (905) 574-3301. Fax: (905) 575-7320. E-mail: crotstei@fhs.mcmaster.ca.

TABLE 1. Comparative in vitro activities of antimicrobial agents

Microorganism	Antimicrobial agent	MIC (mg/liter)			% Susceptible
		Range	50%	90%	
Staphylococcus aureus					
Methicillin susceptible (n = 42)	Amoxicillin-clavulanic acid	≤0.12–4	2	2	100
	Cefuroxime	0.5–2	2	2	100
	Azithromycin	0.5–>32	1	>32	79
	Ciprofloxacin	≤0.12–4	0.5	1	90
	Gemifloxacin	0.008–0.25	0.015	0.03	—[a]
	Grepafloxacin	≤0.06–>8	≤0.06	0.12	97
	Moxifloxacin	≤0.08–1	0.03	0.12	—
	Ofloxacin	≤0.25–8	0.5	1	97
	Sparfloxacin	≤0.06–4	≤0.06	0.25	98
	Trovafloxacin	≤0.03–0.25	≤0.03	≤0.03	100
Methicillin resistant (n = 49)	Amoxicillin-clavulanic acid	4–>16	>16	>16	2
	Cefuroxime	4–>32	>32	>32	4
	Azithromycin	1–>32	>32	>32	8
	Ciprofloxacin	0.25–>16	>16	>16	2
	Gemifloxacin	0.015–16	2	8	—
	Grepafloxacin	≤0.06–>8	>8	>8	2
	Moxifloxacin	0.03–4	2	4	—
	Ofloxacin	≤0.25–>32	16	32	2
	Sparfloxacin	≤0.06–>8	8	>8	2
	Trovafloxacin	≤0.03–8	1	2	61
Staphylococcus epidermidis					
Methicillin susceptible (n =22)	Amoxicillin-clavulanic acid	≤0.12–1	0.25	1	100
	Cefuroxime	≤0.25–1	0.5	0.5	100
	Azithromycin	0.5–>32	1	>32	59
	Ciprofloxacin	≤0.12–0.5	0.25	0.5	100
	Gemifloxacin	≤0.004–0.03	0.015	0.03	—
	Grepafloxacin	≤0.06–0.5	0.12	0.12	100
	Moxifloxacin	≤0.008–0.12	0.06	0.12	—
	Ofloxacin	≤0.25–2	0.5	0.5	100
	Sparfloxacin	≤0.06–0.5	0.12	0.12	100
	Trovafloxacin	≤0.03–0.06	≤0.03	0.06	100
Methicillin resistant (n = 32)	Amoxicillin-clavulanic acid	1–16	4	8	82
	Cefuroxime	≤0.25–>32	4	8	91
	Azithromycin	0.5–>32	>32	>32	12
	Ciprofloxacin	≤0.12–>16	16	>16	19
	Gemifloxacin	≤0.004–8	0.5	2	—
	Grepafloxacin	≤0.06–>8	>8	>8	25
	Moxifloxacin	≤0.08–8	1	4	—
	Ofloxacin	0.5–32	16	32	25
	Sparfloxacin	≤0.06–>8	8	8	22
	Trovafloxacin	≤0.03–16	2	8	44
Staphylococcus haemolyticus (n = 10)	Amoxicillin-clavulanic acid	≤0.12–>16	>16	>16	30
	Cefuroxime	0.5–>32	>32	>32	30
	Azithromycin	0.5–>32	>32	>32	10
	Ciprofloxacin	0.5–>16	16	>16	20
	Gemifloxacin	0.008–16	1	2	—
	Grepafloxacin	≤0.06–>8	8	>8	20
	Moxifloxacin	0.06–8	2	4	—
	Ofloxacin	1–>32	16	>32	20
	Sparfloxacin	0.12–>8	8	>8	20
	Trovafloxacin	≤0.03–16	1	4	50
Staphylococcus hominis (n = 10)	Amoxicillin-clavulanic acid	≤0.12–16	1	16	80
	Cefuroxime	≤0.25–>32	1	>32	80
	Azithromycin	≤0.25–>32	1	>32	50
	Ciprofloxacin	≤0.12–>16	0.25	>16	60
	Gemifloxacin	≤0.004–2	0.03	0.5	—
	Grepafloxacin	≤0.06–>8	0.12	>8	60
	Moxifloxacin	≤0.008–4	0.06	0.5	—
	Ofloxacin	≤0.25–>32	0.5	32	60
	Sparfloxacin	≤0.06–>8	0.25	>8	60
	Trovafloxacin	≤0.03–16	≤0.03	1	90
Miscellaneous coagulase-negative *Staphylococcus* species (n = 13)	Amoxicillin-clavulanic acid	≤0.12–16	0.25	2	92
	Cefuroxime	≤0.25–>32	0.5	32	84
	Azithromycin	≤0.25–>32	0.5	>32	69
	Ciprofloxacin	≤0.12–>2	0.25	0.5	92
	Gemifloxacin	≤0.004–0.06	0.015	0.03	—
	Grepafloxacin	≤0.06–>0.5	0.12	0.12	100

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TABLE 1—*Continued*

Microorganism	Antimicrobial agent	MIC (mg/liter)			% Susceptible
		Range	50%	90%	
	Moxifloxacin	≤0.008–0.5	0.06	0.12	—
	Ofloxacin	≤0.25–>4	0.5	1	92
	Sparfloxacin	≤0.06–0.5	0.12	0.25	100
	Trovafloxacin	≤0.03–0.25	≤0.03	0.06	100
Streptococcus pneumoniae					
Penicillin susceptible (n = 22)	Amoxicillin-clavulanic acid	≤0.015–0.06	≤0.015	≤0.015	100
	Cefuroxime	≤0.12	≤0.12	≤0.12	100
	Azithromycin	≤0.03–0.12	0.06	0.06	100
	Ciprofloxacin	0.5–4	1	2	77
	Gemifloxacin	≤0.004–0.03	0.015	0.03	—
	Grepafloxacin	0.06–0.5	0.12	0.25	100
	Moxifloxacin	0.06–0.25	0.12	0.25	—
	Ofloxacin	1–4	2	2	91
	Sparfloxacin	0.12–0.5	0.25	0.5	100
	Trovafloxacin	0.06–0.25	0.12	0.12	100
Penicillin intermediate (n = 13)	Amoxicillin-clavulanic acid	0.03–2	0.25	2	70
	Cefuroxime	≤0.12–4	0.5	4	54
	Azithromycin	0.06–>4	0.06	4	84
	Ciprofloxacin	0.5–2	1	2	85
	Gemifloxacin	0.008–0.03	0.015	0.03	—
	Grepafloxacin	0.12–0.25	0.25	0.25	100
	Moxifloxacin	0.06–0.12	0.12	0.12	—
	Ofloxacin	1–2	2	2	100
	Sparfloxacin	0.12–0.5	0.25	0.5	100
	Trovafloxacin	≤0.03–0.12	0.12	0.12	100
Penicillin resistant (n = 10)	Amoxicillin-clavulanic acid	1–>2	2	2	0
	Cefuroxime	4–8	4	8	0
	Azithromycin	≤0.03–>4	0.5	>4	50
	Ciprofloxacin	0.5–2	1	1	90
	Gemifloxacin	≤0.004–0.03	0.015	0.03	—
	Grepafloxacin	0.12–0.25	0.25	0.25	100
	Moxifloxacin	0.06–0.12	0.12	0.12	—
	Ofloxacin	1–2	2	2	100
	Sparfloxacin	0.25–0.5	0.25	0.5	100
	Trovafloxacin	≤0.03–0.12	0.12	0.12	100
Enterococcus species					
Penicillin and vancomycin susceptible (n = 31)[b]	Amoxicillin-clavulanic acid	0.5–1	1	1	100
	Cefuroxime	16–>32	>32	>32	0
	Azithromycin	0.5–>32	8	>32	3
	Ciprofloxacin	0.25–>16	2	>16	45
	Gemifloxacin	0.015–4	0.06	2	—
	Grepafloxacin	0.12–>8	0.5	>8	67
	Moxifloxacin	0.06–16	0.25	4	—
	Ofloxacin	1–>32	4	32	41
	Sparfloxacin	0.25–>8	1	>8	38
	Trovafloxacin	0.06–16	0.25	4	84
Penicillin- resistant, vancomycin susceptible (n = 29)[c]	Amoxicillin-clavulanic	0.25–>16	4	>16	50
	Cefuroxime	>32	>32	>32	0
	Azithromycin	8–>32	>32	>32	0
	Ciprofloxacin	4>16	>16	>16	0
	Gemifloxacin	2–>128	8	>128	—
	Grepafloxacin	4–>8	>8	>8	0
	Moxifloxacin	2–>16	16	>16	—
	Ofloxacin	8–>32	>32	>32	0
	Sparfloxacin	2–>8	>8	>8	0
	Trovafloxacin	2–>16	16	>16	0
E. faecium, penicillin and vancomycin resistant (n = 33)	Amoxicillin-clavulanic acid	1–>16	>16	>16	6
	Cefuroxime	>32	>32	>32	0
	Azithromycin	16–>32	>32	>32	0
	Ciprofloxacin	>16	>16	>16	0
	Gemifloxacin	1–>128	64	>128	—
	Grepafloxacin	>8	>8	>8	0
	Moxifloxacin	4–>16	>16	>16	—
	Ofloxacin	>32	>32	>32	0
	Sparfloxacin	>8	>8	>8	0
	Trovafloxacin	2–>16	16	>16	0

[a] No established susceptibility breakpoints are available for gemifloxacin and moxifloxacin.
[b] *E. faecalis*, 21; *E. faecium*, 10.
[c] *E. faecalis*, 11; *E. faecium*, 18.

cocci. Appropriate quality control strains were included in each run of daily testing. These included *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, and *E. faecalis* ATCC 29212. The recorded MICs of all of the antimicrobial agents were the lowest concentrations that completely inhibited visible growth of the test strain. Antimicrobial agent concentrations that inhibited growth of 50% (MIC_{50}) and 90% (MIC_{90}) of the strains and percentages of organisms susceptible were calculated in accordance with the current National Committee for Clinical Laboratory Standards interpretive breakpoints for amoxicillin-clavulanic acid, cefuroxime, azithromycin, ciprofloxacin, and ofloxacin (9). For all isolates, we used a susceptibility breakpoint of ≤1 mg/liter for trovafloxacin. For sparfloxacin, a susceptibility breakpoint of ≤0.5 mg/liter was employed, while ≤2 mg/liter was the breakpoint used for ofloxacin. In contrast, for pneumococcal and enterococcal isolates, the breakpoint for grepafloxacin susceptibility was ≤0.5 mg/liter. However, for staphylococcal isolates, the breakpoint for grepafloxacin-susceptible strains was ≤1 mg/liter. Because no approved susceptibility breakpoints are available for gemifloxacin and moxifloxacin, the percentages of organisms susceptible to these two antimicrobial agents were not recorded.

The phenotypic distribution of the bloodstream isolates was as follows: methicillin-susceptible *S. aureus*, 42; methicillin-resistant *S. aureus* (MRSA), 49; penicillin-susceptible *S. pneumoniae* (PSSP), 22; penicillin-intermediate *S. pneumoniae* (PISP), 13; penicillin-resistant *S. pneumoniae* (PRSP), 10; penicillin- and vancomycin-susceptible enterococci (PSVSE), 31 (21 *E. faecalis* and 10 *E. faecium*); penicillin-resistant and vancomycin-susceptible enterococci (PRVSE), 29 (11 *E. faecalis* and 18 *E. faecium*); penicillin- and vancomycin-resistant enterococci 33 (all *E. faecium* isolates); methicillin-susceptible *Staphylococcus epidermidis* (MSSE), 22; methicillin-resistant *S. epidermidis* (MRSE), 32; *Staphylococcus haemolyticus*, 10; *Staphylococcus hominis*, 10; and coagulase-negative *Staphylococcus species* (CNS), 13.

The susceptibility results, expressed as MIC ranges, MIC_{50}s, MIC_{90}s, and percentages susceptible, are presented in Table 1. Of the drugs tested, gemifloxacin was the most active against PISP, PRSP, MSSE, and coagulase-negative *Staphylococcus* species, attaining MIC_{90}s of ≤0.03 mg/liter, while amoxicillin-clavulanic acid was the most potent against PSVSE and PRVSE. Gemifloxacin also proved to be active against MRSE, *S. hominis*, *S. haemolyticus*, and PSVSE, with MIC_{90}s of ≤2 mg/liter. Trovafloxacin and moxifloxacin, in that order the next most potent fluoroquinolones, were fourfold less potent against PSSP, PISP, and PRSP than gemifloxacin and two- to fourfold less active against MSSE, MRSE, *S. haemolyticus*, and *S. hominis* than gemifloxacin. However, trovafloxacin exhibited the lowest MIC_{90}s for methicillin-susceptible and -resistant *S. aureus*, ≤0.03 and 2 mg/liter, respectively, in comparison with gemifloxacin (0.03 and 8 mg/liter) and moxifloxacin (0.1 and 4 mg/liter). None of the fluoroquinolones exhibited any activity against PRVSE or penicillin- and vancomycin-resistant enterococci.

Among the fluoroquinolones tested, gemifloxacin demonstrated the most potent in vitro activity against commonly encountered PSSP, PISP, and PRSP bloodstream isolates. It also had significant activity against MSSE, MRSE, *S. haemolyticus*, and *S. hominis* but was not as active as trovafloxacin against *S. aureus* isolates. None of the fluoroquinolones tested appears to offer any clinically important activity against penicillin-resistant enterococcal strains. An assessment of gemifloxacin's clinical utility for gram-positive coccus infections must await comparative trails in humans.

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