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In Vitro Activity of Gemifloxacin against 11,311 Clinical Bacterial Isolates collected from the Latin American Region.

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ABSTRACT

Background. The in vitro activity of gemifloxacin (GEMI), a new fluoroquinolone (FQ) with enhanced activity against Gram-positive aerobes, was evaluated in comparison with those of FQs and other antimicrobial agents.

Methods. A total of 4,975 Gram-positive cocci and 6,336 Gram-negative bacilli recently collected from the Latin American region were evaluated. They were isolated from diverse body sites of infection between January 1998 and December 2001. The susceptibility (S) to multiple antimicrobial agents was tested by broth microdilution method according to the NCCLS (2000) recommendations. Quality control was performed using five ATCC strains.

Results. Among the members of the family Enterobacteriaceae, GEMI was generally two-to four-fold more active than ciprofloxacin. GEMI demonstrated poor activity against *Acinetobacter* spp. (MIC_{90}, >4 µg/ml) and *P. aeruginosa* (MIC_{90}, 1 µg/ml). However, it showed good activity against *S. maltophilia* (MIC_{90}, 0.5 µg/ml). GEMI exhibited excellent activity against all Gram-positive cocci. All *S. pneumoniae*, including the penicillin- and macrolide-resistant isolates, were inhibited by GEMI at ≤ 0.5 µg/ml. Nearly 88% of the methicillin-resistant *Staphylococcus aureus* were inhibited at ≤ 1 µg/ml of GEMI.

Conclusions. These results indicate that GEMI is a promising FQ with great in vitro potency against a wide range of clinically important pathogenic bacteria, especially Gram-positive cocci.

INTRODUCTION

Gemifloxacin (formerly SB-265805 and LB20304) is a novel naphthridone compound in the fluoroquinolone class of antimicrobial agents. Initial reports have documented remarkable potency against Gram-positive cocci, with an activity 32- to 64-fold greater than that of ciprofloxacin, especially when tested against oxacillin-resistant staphylococci and penicillin-resistant *Streptococcus pneumoniae*. Gemifloxacin was also observed to be active against Enterobacteriaceae, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, anaerobes, vancomycin-resistant enterococci, and *Haemophilus influenzae* [Cormican & Jones, 1997].

Animal studies suggest that gemifloxacin is less epileptogenic than ciprofloxacin. Bioavailability after oral administration is 95.3 and 75% in rats and dogs, respectively. Gemifloxacin is effective for therapy of systemic infections in mice when given by the oral route [Cormican & Jones, 1997; Zhanel et al., 2002]. This study examines the comparative potency and spectrum of gemifloxacin and selected fluoroquinolones tested against clinical isolates from patients hospitalized in several Latin American medical centers.

MATERIALS AND METHODS

Clinical isolates of aerobic bacteria were collected in 12 Latin American laboratories distributed throughout six countries (11 cities): São Paulo, Rio de Janeiro, Florianopolis, Porto Alegre and Brasilia, Brazil; Buenos Aires and San Isidro, Argentina; Santiago (two centers), Chile; Caracas, Venezuela; Medelin, Colombia; and Mexico City, Mexico. The selection of participant centers was based on the principle that they should be representative of resistance patterns in their geographic region. The participant medical centers were directed by a protocol to collect isolates from consecutive patients. A total of 4,975 Gram-positive cocci and 6,336 Gram-negative bacilli recently collected from the Latin American region were evaluated (January 1998 and December 2001).

Antimicrobial susceptibility testing was performed using broth microdilution methods as described by the National Committee for Clinical Laboratory Standards (NCCLS). Antimicrobial agents were obtained from their respective manufactures as laboratory grade powder, and included gemifloxacin, gatifloxacin, levofloxacin, and ciprofloxacin. Quality control measures were utilized by testing *S. pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *P. aeruginosa* ATCC 27853. Breakpoint interpretive criteria used for all comparison agents were those established by the NCCLS [2002], and for gemifloxacin were those suggested by Wise and Andrews [1999].

RESULTS

Table 1. Occurrence of the 20 most frequently isolated pathogens and activity of two fluoroquinolones.

Organisms in rank order	No. of organisms (% of total)	Gemifloxacin $MIC_{50/90}$ (µg/mL)	Gemifloxacin % Susc.[a]	Ciprofloxacin $MIC_{50/90}$ (µg/mL)	Ciprofloxacin % Susc.[a]
1. *S. aureus*	2,792 (24.7)	0.03/1	77.4	0.5/>2	63.9
Oxacillin-susc	1,749 (15.5)	0.03/0.03	99.5	0.25/0.5	94.3
Oxacillin-resist	1,043 (9.2)	1/2	40.5	>2/>2	9.4
2. *E. coli*	1,810 (16.0)	0.03/4	84.4	0.25/>2	82.9
3. *P. aeruginosa*	1,135 (10.0)	1/>4	48.0	0.5/>2	56.2
4. CoNS[b]	1,116 (9.9)	0.03/1	83.3	0.5/>2	56.5
5. *K. pneumoniae*	893 (8.7)	0.03/2	87.4	0.25/>2	87.4
6. *S. pneumoniae*	601 (5.3)	0.03/0.03	100.0	1/2	--
7. *Enterobacter* spp.	519 (4.6)	0.03/>4	76.3	0.25/>2	81.5
8. *Enterococcus* spp.	466 (4.1)	0.06/2	74.9	1/>2	57.1
9. *H. influenzae*	423 (3.7)	0.016/0.03	100.0	≤0.016/0.03	100.0
10. *Acinetobacter* spp.	418 (3.7)	>4/>4	35.2	>2/>2	31.4
11. *Salmonella* spp.	224 (2.0)	0.016/0.12	100.0	≤0.016/0.25	100.0
12. *Shigella* spp.	205 (1.8)	0.016/0.016	100.0	≤0.016/≤0.016	100.0
13. *Proteus* spp.	177 (1.6)	0.06/>4	75.1	0.25/>2	80.2
14. *Serratia* spp.	168 (1.5)	0.12/2	67.3	0.25/>2	82.2
15. *K. oxytoca*	111 (1.0)	0.03/0.5	91.9	0.25/2	88.0
16. *S. maltophilia*	102 (0.9)	0.5/1	75.5	2/>2	47.8
17. *M. catharralis*	86 (0.8)	0.016/0.03	100.0	0.03/0.06	100.0
18. *Citrobacter* spp.	67 (0.6)	0.03/>4	86.6	0.25/>2	85.6
19. *M. morganii*	45 (0.4)	0.06/>4	71.1	0.25/>2	71.9
20. *B. cepacia*	27 (0.2)	0.25/2	63.0	1/>2	65.2

a. Susceptibility as defined by the NCCLS or Wise et al. [1999].
b. CoNS = coagulase-negative staphylococci.

Table 2. Antimicrobial activity and spectrum of gemifloxacin in comparison to selected fluoroquinolones against the most frequently isolated Gram-positive cocci.

Organisms (no. tested)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	% Susceptible
S. aureus (2,792)			
Gemifloxacin	0.03	1	77.4
Gatifloxacin	0.12	2	91.4
Ciprofloxacin	0.5	>2	63.9
CoNS (1,116)			
Gemifloxacin	0.03	1	83.3
Gatifloxacin	0.12	2	94.6
Ciprofloxacin	0.5	>2	56.5
S. pneumoniae (601)			
Gemifloxacin	0.03	0.03	100.0
Gatifloxacin	0.25	0.5	99.7
Levofloxacin	1	1	99.7
Ciprofloxacin	1	2	---
Enterococcus spp. (466)			
Gemifloxacin	0.06	2	74.9
Gatifloxacin	0.5	>4	76.8
Ciprofloxacin	1	>2	57.1

- A total of 11,311 clinical bacterial isolates were collected and the majority of isolates were Gram-negative bacilli (56%). The main infection sites were bacteremia, lower respiratory tract, urinary tract and skin/soft tissue infection.
- Gemifloxacin was the most active compound against Gram-positive cocci (16- to 32-fold more potent than ciprofloxacin and 4- to 8-fold more potent than gatifloxacin; Tables 1 and 2).
- *S. aureus* was the most frequently isolated species (24.7% of total), and 37.5% of isolates were considered MRSA. Gemifloxacin was highly active against oxacillin-susceptible strains (MIC_{90}, 0.03 µg/mL; 99.5% susceptibilty); however, oxacillin-resistant strains showed much higher gemifloxacin MICs (MIC_{90}, 2 µg/mL; 40.5% susceptibility) (Table 1).

Table 3. Antimicrobial activity and spectrum of gemifloxacin in comparison to selected fluoroquinolones against the most frequently isolated Gram-negative bacilli.

Pathogen (no. tested)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	% Susceptible
E. coli (1,810)			
Gemifloxacin	0.03	4	84.4
Gatifloxacin	0.03	>4	83.5
Levofloxacin	0.03	>4	83.3
Ciprofloxacin	0.25	>2	82.9
P. aeruginosa (1,135)			
Gemifloxacin	1	>4	48.0
Gatifloxacin	2	>4	53.0
Levofloxacin	1	>4	55.4
Ciprofloxacin	0.5	>2	56.2
K. pneumoniae (893)			
Gemifloxacin	0.03	2	87.4
Gatifloxacin	0.06	2	90.0
Levofloxacin	0.06	2	89.6
Ciprofloxacin	0.25	>2	87.4
Enterobacter spp. (519)			
Gemifloxacin	0.03	>4	76.3
Gatifloxacin	0.06	>4	81.6
Levofloxacin	0.12	>4	80.7
Ciprofloxacin	0.25	>2	81.5
H. influenzae (423)			
Gemifloxacin	0.016	0.03	100.0
Gatifloxacin	0.03	0.03	100.0
Levofloxacin	0.03	0.03	100.0
Ciprofloxacin	≤0.016	0.03	100.0
Acinetobacter spp. (418)			
Gemifloxacin	>4	>4	35.2
Gatifloxacin	4	>4	35.5
Levofloxacin	>4	>4	33.3
Ciprofloxacin	>2	>2	31.4
Serratia spp.(168)			
Gemifloxacin	0.12	2	67.3
Gatifloxacin	0.25	>4	81.4
Levofloxacin	0.12	>4	82.6
Ciprofloxacin	0.25	>2	82.2
S. maltophilia (102)			
Gemifloxacin	0.5	1	75.5
Gatifloxacin	0.5	2	94.8
Levofloxacin	0.5	2	91.8
Ciprofloxacin	2	>2	47.8

- Gemifloxacin was highly active against *S. pneumoniae* strains (MIC_{90}, 0.03 µg/mL; 100% susceptibility) and was 32-fold more potent than levofloxacin or ciprofloxacin (MIC_{50}, 1 µg/mL), and four-fold more potent than gatifloxacin (MIC_{50}, 0.25 µg/mL).
- All fluoroquinolones evaluated showed similar potency and spectrum against Gram-negative bacilli, with a few exceptions (*Serratia* spp.; Table 3). Ciprofloxacin was less active than the other compounds against *S. maltophilia* and *Acinetobacter* spp. isolates were resistant to these compounds (31.4% – 47.8% susceptibility).
- *H. influenzae* isolates were highly susceptible to all fluoroquinolones evaluated.

CONCLUSIONS

- When compared to other fluoroquinolone compounds, gemifloxacin has improved potency and spectrum against Gram-positive cocci with a modest loss of in vitro activity against Gram-negative bacilli using applied breakpoints.
- The excellent gemifloxacin spectrum against bacterial pathogens responsible for community-acquired respiratory tract infections indicates its area of greatest value for use in Latin America.

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