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Gemifloxacin Demonstrates Potent *In Vitro* Activity Against Global Isolates of Antibiotic-resistant *Streptococcus pneumoniae*

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Abstract

RTIs of bacterial aetiology are commonly attributable to *Streptococcus pneumoniae*. Concern has arisen globally in the last decade regarding the dramatic increase in prevalence of penicillin- and macrolide-resistant isolates of *S. pneumoniae*. In addition, quinolone resistance among pneumococci has recently been reported. Gemifloxacin (SB-265805) is an enhanced-affinity quinolone with potent *in vitro* activity against *S. pneumoniae*. In the current study, the *in vitro* activity of gemifloxacin was determined for isolates of *S. pneumoniae* resistant to penicillin, azithromycin, clarithromycin and ofloxacin.

Isolates were collected during 1997–99 from a variety of clinical sources. Each isolate was identified using local laboratory criteria by 93 study centres in 16 European, two North American and three South American countries. MICs were determined in each country at one or more central laboratories using commercially prepared microbroth dilution panels according to NCCLS guidelines.

Among penicillin-resistant isolates (n = 411), MIC_{90}s for gemifloxacin, levofloxacin, ofloxacin, clarithromycin and azithromycin were 0.03, 1, 2, >16 and >64 mg/L, respectively. For azithromycin- and clarithromycin-resistant isolates (n = 714), MIC_{90}s for gemifloxacin, levofloxacin, ofloxacin and penicillin were 0.03, 1, 2 and 4 mg/L, respectively. For ofloxacin-intermediate and -resistant isolates (n = 142) MIC_{90}s for gemifloxacin, levofloxacin, penicillin, clarithromycin and azithromycin were 0.12, 2, 4, >16 and >64 mg/L, respectively.

Gemifloxacin was the most potent antimicrobial tested against penicillin-, azithromycin-, clarithromycin- and ofloxacin-resistant *S. pneumoniae*. The gemifloxacin MIC_{90} for ofloxacin-non-susceptible isolates was 0.12 mg/L compared with 2 mg/L for levofloxacin. The study data suggest that gemifloxacin may find clinical utility in the treatment of RTIs attributable to either resistant or sensitive *S. pneumoniae* strains.

Introduction

Streptococcus pneumoniae is an important bacterial pathogen in upper and lower RTIs, such as community-acquired pneumonia, acute exacerbations of chronic bronchitis, otitis media and sinusitis. The rapid emergence of penicillin, macrolide and multi-drug resistance among isolates of *S. pneumoniae* during the 1990s has encouraged the development, testing and marketing of new antimicrobials, such as respiratory fluoroquinolones. It has also resulted in new recommendations for the treatment of community-acquired pneumonia[1] and has necessitated ongoing antimicrobial resistance surveillance studies which can contribute to the selection of appropriate empiric antibiotic therapy. New quinolones are now recommended for the treatment of RTI due to *S. pneumoniae*, particularly for isolates resistant to β-lactam antimicrobials.

Gemifloxacin (SB-265805), an enhanced-affinity quinolone, has previously been reported to demonstrate excellent *in vitro* activity against isolates of clinically significant Gram positive cocci, including *S. pneumoniae*. In addition, gemifloxacin has excellent activity against Gram negative bacilli and Gram positive anaerobes, and modest potency against non-fermentative Gram negative bacilli. Gemifloxacin has also been demonstrated to retain potent activity against isolates of *S. pneumoniae* harbouring target site mutations (*gyrA*, *gyrB*, *parC*, *parE*) and/or efflux mechanisms that significantly elevate MICs to other currently marketed fluoroquinolones, most noticeably ciprofloxacin. The current study extends previous reports and presents comparative gemifloxacin susceptibility data using a collection of 2632 recent international isolates of *S. pneumoniae*, including 142 ofloxacin-intermediate and -resistant isolates.

Materials and Methods

S. pneumoniae Isolates

- Between September 1997 and August 1999, 93 study sites in 21 countries prospectively collected isolates, with most sites contributing up to 50 isolates of *S. pneumoniae* for study. Isolate inclusion was independent of medical history, patient age or gender.
- Each isolate was identified as *S. pneumoniae* and deemed to be a significant pathogen.
- The *S. pneumoniae* isolates described here are components of a larger prospective international surveillance study of the activity of gemifloxacin against selected aerobic Gram positive and Gram negative pathogens.
- Isolate collection, processing, transport, antimicrobial susceptibility testing methods and the construction of a centralised database to record worldwide antimicrobial susceptibility testing results were co-ordinated by Laboratories International for Microbiology Studies, International Health Management Associates (IHMA Inc) (Rolling Meadows, IL, USA).
- Available demographic information included patient age, specimen source and in *versus* out patient information.

Participating Study Centres

Country	Sites (n)	*S. pneumoniae* (n)	Country	Sites (n)	*S. pneumoniae* (n)
Argentina	5	77	Italy	3	198
Austria	7	49	Luxembourg	1	43
Belgium	6	43	Mexico	7	58
Brazil	6	45	Netherlands	16	42
Canada	12	73	Poland	1	50
Denmark	1	49	Spain	1	302
Finland	1	40	Sweden	1	50
France	5	481	Switzerland	1	49
Germany	6	311	UK	2	192
Greece	8	85	USA	3	347
Hungary	1	48			

Antimicrobial Susceptibility Testing

- MICs were determined by the NCCLS recommended broth microdilution testing method.[2] The microdilution panels used in this study were purchased from two companies: MicroScan® (Dade Behring Inc, Sacramento, CA, USA) and Sensititre® (Trek Diagnostics Inc, Westlake, OH, USA), and utilised identical antimicrobial dilution configurations. Gemifloxacin was supplied by SmithKline Beecham (Collegeville, PA, USA) and the 10 comparative antimicrobials by their respective manufacturers or the panel manufacturer. Appropriate broth media were also provided directly by the panel manufacturers.
- MICs were determined in each participating country at one or more designated laboratories.
- The antimicrobial breakpoints for *S. pneumoniae* used for data analysis were those recommended by the NCCLS for broth dilution susceptibility testing.[3]
- Each designated laboratory performed daily quality control testing that included *S. pneumoniae* ATCC 49619. Test isolate results were accepted into the final analysis only if the quality control isolate MIC was within the acceptable range defined by NCCLS guidelines.[3]

Results

The results are shown in Tables 1–3.

- Overall rates of resistance to penicillin, cefuroxime, azithromycin, clarithromycin and trimethoprim/sulphamethoxazole (TMP/SMX) were considerable, at 15.6%, 20.5%, 26.0%, 27.1% and 24.4%, respectively (Table 1). In comparison, overall rates of trovafloxacin, levofloxacin, grepafloxacin and ofloxacin resistance were much lower at 0.3%, 0.3%, 0.6% and 0.7%, respectively.
- Ofloxacin-non-susceptible isolates were primarily ofloxacin intermediate (MIC 4 mg/L) and retained susceptibility to the other fluoroquinolones tested.
- Most *S. pneumoniae* isolates with ofloxacin MICs ≥16 mg/L were resistant to grepafloxacin, levofloxacin and trovafloxacin. The activity of gemifloxacin against the same isolates was notably more potent, with MICs all ≤0.5 mg/L.
- The gemifloxacin MIC for all isolates of *S. pneumoniae* tested (n = 2632) was ≤0.5 mg/L.
- Resistance to grepafloxacin, levofloxacin or trovafloxacin was unrelated to penicillin, azithromycin and clarithromycin MICs.
- Based on MIC_{90} comparisons, gemifloxacin was 8-, 16-, 16-, 32- and 64-fold more potent than trovafloxacin, grepafloxacin, levofloxacin, ciprofloxacin and ofloxacin against ofloxacin-intermediate and -resistant isolates.
- Ofloxacin-intermediate and -resistant isolates were recovered at similar rates from European (5.8%, 117/2032), North American (4.1%, 17/420) and South American (4.4%, 8/180) study centres.
- Age data were provided for 2491 of the 2632 patients. Patients ≤16 years of age accounted for 43.5% (n = 1083) of isolates, while 33.2% (n = 828) and 23.3% (n = 580) of patients were aged 17–64 years and ≥65 years, respectively. Ofloxacin-intermediate and -resistant *S. pneumoniae* were isolated from 5.1% (55/1083) of patients ≤16 years of age, from 4.0% (33/828) of patients 17–64 years of age and from 6.6% (38/580) of patients ≥65 years of age.

Conclusions

- Rates of resistance to respiratory fluoroquinolones were <1% for 2632 global isolates of *S. pneumoniae*.
- Rates of resistance to penicillin (MIC >1 mg/L; 15.6%), azithromycin (MIC >1 mg/L; 26.0%) and clarithromycin (MIC >0.5 mg/L; 27.1%) were considerably higher in the same collection of *S. pneumoniae*.
- Most *S. pneumoniae* isolates with ofloxacin MICs ≥16 mg/L were resistant to grepafloxacin, levofloxacin and trovafloxacin. The activity of gemifloxacin against the same isolates was notably more potent, with MICs all ≤0.5 mg/L.
- Gemifloxacin was the most potent fluoroquinolone tested against all isolates of *S. pneumoniae,* including penicillin-, azithromycin-, clarithromycin- and ofloxacin-resistant isolates.
- Gemifloxacin represents a significant advance compared with currently marketed fluoroquinolones, especially in terms of its potential for the treatment of pneumococcal infections. The activity of gemifloxacin against *S. pneumoniae*, in addition to the common Gram negative respiratory tract pathogens *Haemophilus influenzae* and *Moraxella catarrhalis*, suggests a definitive role in the therapy of RTIs due to resistant and sensitive strains of *S. pneumoniae*.

References

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2 National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*. Villanova, PA, USA: NCCLS, 1997: approved standard M7-A4.
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Table 1. *In Vitro* Activities of Gemifloxacin and 10 Comparative Antimicrobials Against 2632 Isolates of *S. pneumoniae* Collected from Europe, North America and South America

Antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	%-S[a]	%-I[a]	%-R[a]
Penicillin	0.03	2	0.015–>16	62.0	22.3	15.6
Cefuroxime	0.06	4	0.06–>64	75.4	4.1	20.5
Azithromycin	0.06	>64	0.06–>64	72.0	2.1	26.0
Clarithromycin	0.03	>16	0.015–>16	71.2	1.7	27.1
TMP/SMX[b]	0.25	8	0.06–>64	64.3	11.4	24.4
Ciprofloxacin	1	2	0.015–>16	–	–	–
Grepafloxacin	0.12	0.25	0.015–16	99.2	0.2	0.6
Levofloxacin	1	1	0.015–16	99.5	0.2	0.3
Ofloxacin	2	2	0.06–64	94.6	4.7	0.7
Trovafloxacin	0.12	0.25	0.015–>16	99.6	0.1	0.3
Gemifloxacin	0.015	0.03	0.001–0.5	–	–	–

[a]NCCLS recommended breakpoints (mg/L) were used to group isolates into %-susceptible (%-S), %-intermediate (%-I) and %-resistant (%-R) categories.[3] Susceptible, intermediate and resistant breakpoints have not been published by the NCCLS for ciprofloxacin and gemifloxacin. European study centres provided 2032 isolates while 420 and 180 isolates, respectively, were tested from study centres in North and South America
[b]TMP/SMX ratio tested was 1:19

Table 2. *In Vitro* Activities of Gemifloxacin and 10 Comparative Antimicrobials Against Isolates of *S. pneumoniae* Intermediate and Resistant to Penicillin, Macrolides and Ofloxacin

Phenotype (n)	Antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range (mg/L)	%-S[a]	%-I[a]	%-R[a]
PI + PR[b] (999)	Penicillin	1	4	0.12–>16	–	58.9	41.1
	Cefuroxime	4	8	0.06–>64	36.0	10.3	53.7
	Azithromycin	2	>64	0.06–>64	43.8	4.6	51.6
	Clarithromycin	1	>16	0.015–>16	43.9	3.1	53.0
	TMP/SMX	4	8	0.06–>64	27.9	16.6	55.5
	Ciprofloxacin	1	2	0.015–>16	–	–	–
	Grepafloxacin	0.12	0.25	0.015–16	98.9	0.3	0.8
	Levofloxacin	1	1	0.015–16	99.3	0.3	0.4
	Ofloxacin	2	2	0.06–64	91.4	7.7	0.9
	Trovafloxacin	0.12	0.25	0.015–>16	99.5	0.1	0.4
	Gemifloxacin	0.015	0.03	0.001–0.5	–	–	–
MI + MR[c] (714)	Penicillin	1	4	0.015–>16	24.3	36.8	38.9
	Cefuroxime	2	8	0.06–>64	42.6	8.0	49.4
	Azithromycin	>64	>64	1–>64	–	6.9	93.1
	Clarithromycin	>16	>16	0.5–>16	–	4.2	95.8
	TMP/SMX	2	8	0.06–>64	35.3	15.0	49.7
	Ciprofloxacin	1	2	0.015–>16	–	–	–
	Grepafloxacin	0.12	0.25	0.015–16	98.6	0.1	1.3
	Levofloxacin	0.5	1	0.015–16	98.6	0.6	0.8
	Ofloxacin	2	2	0.06–64	92.3	6.4	1.3
	Trovafloxacin	0.12	0.25	0.015–>16	99.1	0.1	0.8
	Gemifloxacin	0.015	0.03	0.001–0.5	–	–	–
OI + OR[d] (142)	Penicillin	0.12	4	0.015–>16	39.4	38.1	22.5
	Cefuroxime	0.12	8	0.06–>64	69.0	5.6	25.4
	Azithromycin	0.25	>64	0.06–>64	59.2	2.1	38.7
	Clarithromycin	0.06	>16	0.015–>16	55.6	4.2	40.2
	TMP/SMX	0.5	8	0.06–>64	54.9	14.1	31.0
	Ciprofloxacin	2	4	0.015–>16	–	–	–
	Grepafloxacin	0.25	2	0.03–16	87.9	2.2	9.9
	Levofloxacin	1	2	0.015–16	90.2	3.5	6.3
	Ofloxacin	4	8	4–64	–	86.6	13.4
	Trovafloxacin	0.25	1	0.015–>16	95.1	0.0	4.9
	Gemifloxacin	0.06	0.12	0.001–0.5	–	–	–

[a]Breakpoints (mg/L) used to define %-susceptible (%-S), %-intermediate (%-I) and %-resistant (%-R) categories are those recommended by the NCCLS.[3] Susceptible, intermediate and resistant breakpoints have not been published by the NCCLS for ciprofloxacin and gemifloxacin
[b]Penicillin-intermediate (PI) and penicillin-resistant (PR) isolates
[c]Macrolide-intermediate (MI) and macrolide-resistant (MR) isolates. Only isolates intermediate/resistant to azithromycin and intermediate/resistant to clarithromycin were included
[d]Ofloxacin-intermediate (OI) and ofloxacin-resistant (OR) isolates

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Table 3. *In Vitro* Activity of Fluoroquinolones Against 142 Isolates of *S. pneumoniae* with Ofloxacin MICs ≥4 mg/L. The Number of Isolates Inhibited (and Cumulative % Inhibited) are Given for Each Fluoroquinolone Tested

Fluoroquinolone	MIC (mg/L)														
	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16	≥32
Ciprofloxacin	–	–	1 (0.7)	0 (0.7)	0 (0.7)	0 (0.7)	1 (1.4)	1 (2.1)	32 (24.7)	47 (57.8)	49 (92.3)	2 (93.7)	4 (96.5)	5 (100)	–
Grepafloxacin	–	–	0	6 (4.3)	18 (17.0)	19 (30.5)	48 (64.5)	33 (87.9)	3[a] (90.1)	3 (92.2)	4 (95.0)	4 (97.9)	3 (100)	–	–
Levofloxacin	–	–	1 (0.7)	0 (0.7)	0 (0.7)	1 (1.4)	1 (2.1)	7 (7.0)	88 (69.0)	30 (90.1)	5[a] (93.7)	4 (96.5)	5 (100)	–	–
Ofloxacin	–	–	–	–	–	–	–	–	–	–	123[a] (86.2)	10 (93.6)	1 (94.4)	0 (94.4)	8 (100)
Trovafloxacin	–	–	2 (1.4)	1 (2.1)	3 (4.2)	50 (39.4)	62 (83.1)	11 (91.0)	6 (95.1)	0[a] (95.1)	3 (97.2)	3 (99.3)	0 (99.3)	1 (100)	–
Gemifloxacin	1 (0.7)	2 (2.1)	18 (14.9)	49 (49.6)	48 (83.7)	12 (92.2)	6 (96.5)	6 (100)	0	0	0	0	0	0	0

[a]Established intermediate interpretative standards for susceptibility as defined by the NCCLS[3]