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In Vitro Activity of Gemifloxacin Against *Enterobacteriaceae* Isolated in North America

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Abstract

Background: Gemifloxacin (SB-265805) is a novel fluoroquinolone that has previously demonstrated significant *in vitro* activity against a broad range of Gram negative pathogens. The activity of gemifloxacin was compared with that of other fluoroquinolones against a broad range of *Enterobacteriaceae* isolates from 15 sites in the USA and Canada. Methods: A variety of clinical isolates, collected during 1997–1999, was identified at each participating site using local laboratory criteria. MICs were determined at a central testing site in each country using Sensititre prepared broth microdilution panels according to NCCLS guidelines and manufacturer instructions. Conclusion: Against the majority of *Enterobacteriaceae*, gemifloxacin was as active as all other quinolones tested. The gemifloxacin MIC_{90} (0.03 µg/ml) against *Escherichia coli* (358) was lower than that for ciprofloxacin (0.5 µg/ml), levofloxacin (0.5 µg/ml), ofloxacin (0.5 µg/ml), grepafloxacin (0.12 µg/ml) and trovafloxacin (0.06 µg/ml).

Introduction

Gemifloxacin is an enhanced-affinity fluoroquinolone with potent activity against both Gram negative bacteria, such as *Escherichia coli*, *Proteus mirabilis* and *Klebsiella pneumoniae* as well as Gram positive bacteria, such as streptococci and staphylococci.[1–4] To confirm data presented in previous studies with data on recent clinical isolates, the antimicrobial activity of gemifloxacin and comparative agents was determined against 1549 recent clinical isolates of *Enterobacteriaceae* collected in Canada and the USA.

Materials and Methods

Isolates of *Enterobacteriaceae*

- Between September 1997 and August 1999, 12 study sites in Canada and three study sites in the United States each prospectively collected isolates, with most sites contributing up to 50 isolates of aerobic Gram positive and Gram negative pathogens, as well as up to 100 isolates each of *E. coli* and *K. pneumoniae*.
- Isolate inclusion was independent of medical history, patient age or gender.
- Only one isolate was accepted per patient.
- Each isolate was identified and deemed to be a significant pathogen using local laboratory criteria.
- Isolate collection, processing, transport and antimicrobial susceptibility testing methods as well as the construction of a centralized database to record worldwide antimicrobial susceptibility testing results were coordinated by Laboratories International for Microbiology Studies, International Health Management Associates (IHMA) (Rolling Meadows, IL, USA).
- Available demographic information included patient age, specimen source, and in *versus* out patient information.

Antimicrobial Susceptibility Testing

- MICs were determined by the NCCLS recommended broth microdilution testing method.[5] The microdilution panels used in this study were purchased from Sensititre (Trek Diagnostics Inc, Westlake, OH, USA). Gemifloxacin was supplied by SmithKline Beecham (Collegeville, PA, USA) and comparative antimicrobials by their respective manufacturers or the panel manufacturer. Appropriate broth media were also provided directly by the panel manufacturers.[5]
- MICs were determined in each participating country at one designated laboratory.
- The antimicrobial breakpoints used for data analysis were those recommended by the NCCLS for broth dilution susceptibility testing.[6]
- Each designated laboratory performed daily quality control testing that included *E. coli* ATCC 25922, *E. coli* ATCC 35218 and *Staphylococcus aureus* ATCC 29213. Test isolate results were accepted into the final analysis only if the quality control isolate MICs were within the acceptable range defined by NCCLS guidelines.[6]

Participating Study Centers

- In Canada, 12 study centers participated. They were Mount Sinai Hospital, Toronto; Health Sciences Centre, Winnipeg; Calgary Laboratory Services, Calgary; Victoria General Hospital, Victoria; St. Joseph's Health Centre, London; General Hospital, St. John's; Hospital Maisonneuve-Rosemont, Montreal; Moncton Hospital, Moncton; QE II Health Services Centre, Halifax; Ottawa Hospital, Ottawa; Princess Margaret Hospital, Toronto; and Toronto Hospital, Toronto.
- In the USA, three study centers participated. They were Stanford University Hospital, Stanford; Bryn Mawr Hospital, Bryn Mawr; and Evanston Northwestern Healthcare, Evanston.

Results

Results are shown in Tables 1–6.

Table 1. *In Vitro* Activities of Gemifloxacin and Comparative Antimicrobials Against 1549 Isolates of *Enterobacteriaceae* Collected in Canada and the USA

Antimicrobial	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	%-S[a]	%-I[a]	%-R[a]
Ampicillin	32	>64	0.06–>64	29.7	7.3	63.0
Cefuroxime	4	>64	0.06–>64	68.8	7.1	24.1
Gentamicin	0.5	1	0.06–>64	95.0	1.6	3.4
TMP/SMX[b]	0.25	64	0.06–>64	87.6	–	12.4
Ciprofloxacin	0.03	0.5	0.015–>16	93.6	2.1	4.3
Grepafloxacin	0.06	1	0.015–>16	92.4	2.3	5.4
Levofloxacin	0.06	0.5	0.015–>16	95.5	1.4	3.0
Ofloxacin	0.12	2	0.06–>64	92.6	2.3	5.0
Trovafloxacin	0.06	1	0.015–>16	93.8	1.8	4.4
Gemifloxacin	0.03	0.5	0.06–>256	NA[c]	NA[c]	NA[c]

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into %-susceptible (%-S), %-intermediate (%-I) and %-resistant (%-R) categories[6]
[b]TMP/SMX = trimethoprim/sulfamethoxazole; ratio tested was 1:19
[c]Susceptible, intermediate and resistant breakpoints have not been established by the NCCLS

Table 2. *In Vitro* Activities of Gemifloxacin and Comparative Antimicrobials Against 358 Isolates of *E. coli*

Antimicrobial	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	%-S[a]	%-I[a]	%-R[a]
Ampicillin	4	>64	0.5–>64	61.6	1.7	36.7
Cefuroxime	4	16	0.5–>64	89.9	4.2	5.9
Gentamicin	0.5	2	0.12–>64	93.0	1.4	5.6
TMP/SMX[b]	0.25	>64	0.06–>64	82.3	–	17.7
Ciprofloxacin	0.015	0.5	0.015–>16	94.9	0.6	4.5
Grepafloxacin	0.015	0.12	0.015–>16	95.5	0.0	4.5
Levofloxacin	0.03	0.5	0.015–>16	95.5	0.8	3.7
Ofloxacin	0.06	0.5	0.06–>64	95.5	0.0	4.5
Trovafloxacin	0.015	0.06	0.015–>16	95.5	0.6	3.9
Gemifloxacin	0.008	0.03	0.001–32	NA[c]	NA[c]	NA[c]

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into %-susceptible (%-S), %-intermediate (%-I) and %-resistant (%-R) categories[6]
[b]TMP/SMX = trimethoprim/sulfamethoxazole; ratio tested was 1:19
[c]Susceptible, intermediate and resistant breakpoints have not been established by the NCCLS

Table 3. *In Vitro* Activities of Gemifloxacin and Comparative Antimicrobials Against 282 Isolates of *K. pneumoniae*

Antimicrobial	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	%-S[a]	%-I[a]	%-R[a]
Ampicillin	32	>64	0.06–>64	6.4	14.9	78.7
Cefuroxime	2	16	0.12–>64	85.1	8.9	6.0
Gentamicin	0.25	0.5	0.06–>64	97.5	1.4	1.1
TMP/SMX[b]	0.25	2	0.06–>64	91.1	–	8.9
Ciprofloxacin	0.03	0.5	0.015–>16	95.4	1.8	2.8
Grepafloxacin	0.03	0.5	0.015–>16	96.1	0.7	3.2
Levofloxacin	0.06	0.5	0.015–>16	96.5	0.7	2.8
Ofloxacin	0.12	2	0.06–>64	95.4	1.8	2.8
Trovafloxacin	0.06	0.5	0.015–>16	97.5	0.0	2.5
Gemifloxacin	0.03	0.25	0.001–>128	NA[c]	NA[c]	NA[c]

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into %-susceptible (%-S), %-intermediate (%-I) and %-resistant (%-R) categories[6]
[b]TMP/SMX = trimethoprim/sulfamethoxazole; ratio tested was 1:19
[c]Susceptible, intermediate and resistant breakpoints have not been established by the NCCLS

Table 4. *In Vitro* Activities of Gemifloxacin and Comparative Antimicrobials Against 151 Isolates of *Enterobacter cloacae*

Antimicrobial	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	%-S[a]	%-I[a]	%-R[a]
Ampicillin	>64	>64	0.25–>64	14.6	6.0	79.5
Cefuroxime	16	>64	0.25–>64	47.7	11.9	40.4
Gentamicin	0.25	0.5	0.12–>64	96.7	1.3	2.0
TMP/SMX[b]	0.25	2	0.06–>64	92.1	–	7.9
Ciprofloxacin	0.015	0.25	0.015–16	94.0	5.3	0.7
Grepafloxacin	0.03	0.5	0.015–>16	93.4	4.0	2.6
Levofloxacin	0.03	0.5	0.015–16	97.4	2.0	0.7
Ofloxacin	0.06	1	0.06–32	94.0	1.3	4.6
Trovafloxacin	0.03	0.5	0.015–>16	94.7	4.0	1.3
Gemifloxacin	0.015	0.25	0.002–16	NA[c]	NA[c]	NA[c]

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into %-susceptible (%-S), %-intermediate (%-I) and %-resistant (%-R) categories[6]
[b]TMP/SMX = trimethoprim/sulfamethoxazole; ratio tested was 1:19
[c]Susceptible, intermediate and resistant breakpoints have not been established by the NCCLS

Table 5. *In Vitro* Activities of Gemifloxacin and Comparative Antimicrobials Against 140 Isolates of *P. mirabilis*

Antimicrobial	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)	Range (µg/ml)	%-S[a]	%-I[a]	%-R[a]
Ampicillin	1	>64	0.25–>64	82.1	1.4	16.4
Cefuroxime	2	4	0.5–>64	97.1	0.0	2.9
Gentamicin	1	2	0.12–64	94.3	1.4	4.3
TMP/SMX[b]	0.25	4	0.06–>64	83.6	–	16.4
Ciprofloxacin	0.03	0.25	0.015–>16	91.4	2.1	6.4
Grepafloxacin	0.25	2	0.06–>16	89.3	1.4	9.3
Levofloxacin	0.06	0.25	0.015–>16	95.0	1.4	3.6
Ofloxacin	0.12	1	0.06–>64	92.1	2.9	5.0
Trovafloxacin	0.25	1	0.03–>16	90.7	0.0	9.3
Gemifloxacin	0.12	0.5	0.008–128	NA[c]	NA[c]	NA[c]

[a]NCCLS recommended breakpoints (µg/ml) were used to group isolates into %-susceptible (%-S), %-intermediate (%-I) and %-resistant (%-R) categories[6]
[b]TMP/SMX = trimethoprim/sulfamethoxazole; ratio tested was 1:19
[c]Susceptible, intermediate and resistant breakpoints have not been established by the NCCLS

Table 6. Comparison of the *In Vitro* Activities of Gemifloxacin and Other Quinolones Tested Against Isolates of *Enterobacteriaceae*

Enterobacteriaceae (n)	MIC_{90} (µg/ml)					
	GEM	CIP	GRE	LEV	OFL	TRO
C. freundii (131)	2	2	4	4	8	4
E. aerogenes (115)	0.25	0.25	0.5	0.5	1	0.5
E. cloacae (151)	0.25	0.25	0.5	0.5	1	0.5
E. coli (358)	0.03	0.5	0.12	0.5	0.5	0.06
K. oxytoca (126)	0.25	0.25	0.5	0.5	1	0.5
K. pneumoniae (282)	0.25	0.5	0.5	0.5	2	0.5
M. morganii (72)	0.12	0.06	0.25	0.12	0.25	0.5
P. mirabilis (140)	0.5	0.25	2	0.25	1	1
P. penneri (3)[a]	0.25	0.12	0.25	0.12	0.25	0.12
P. vulgaris (23)	0.12	0.03	0.25	0.12	1	0.5
P. rettgeri (6)[a]	0.06	0.03	0.12	0.12	0.25	0.12
P. stuartii (22)	16	16	16	16	32	16
S. liquefaciens (4)[a]	0.015	0.015	0.06	0.03	0.06	0.06
S. marcescens (114)	2	1	4	2	4	4
S. plymuthica (1)[a]	0.008	0.015	0.015	0.015	0.06	0.03
S. sonnei (Group D) (1)[a]	0.015	2	0.25	0.5	4	0.12
Enterobacteriaceae (1549)	0.5	0.5	1	0.5	2	1

[a]If less than 20 isolates were available the mode is reported in place of the MIC_{90}

Conclusions

- Based upon MIC_{90} data, gemifloxacin was as active as levofloxacin and ciprofloxacin, and more active than grepafloxacin, ofloxacin and trovafloxacin against all isolates of *Enterobacteriaceae* tested.
- Gemifloxacin was the most potent antimicrobial tested (MIC_{90} 0.03 µg/ml) against *E. coli*.
- Gemifloxacin was the most potent antimicrobial tested (MIC_{90} 0.25 µg/ml) against *K. pneumoniae*.
- Gemifloxacin and ciprofloxacin were the most potent antimicrobials tested (MIC_{90} 0.25 µg/ml) against *E. cloacae*.
- Gemifloxacin demonstrated potency similar to ciprofloxacin and levofloxacin (MIC_{90} 0.25–0.5 µg/ml) against *P. mirabilis*.

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