In the face of the increasing worldwide problem of antimicrobial resistance, many classes of antimicrobial agents have become less useful for therapy (1). Fluoroquinolones continued to be used for the treatment of various infections, because they are active against both Gram-positive and Gram-negative bacteria (2-4). However, resistance to the second-generation fluoroquinolones has increased against many bacterial species. Gemifloxacin is a new fluoroquinolone under development with enhanced affinity for topoisomerase IV, and DNA gyrase, and has the lowest minimum inhibitory concentrations (MICs) against clinical isolates of \textit{Streptococcus pneumoniae} (5-7). In Korea, resistant bacteria are relatively more prevalent than in other industrialized countries. In this study, we studied the in vitro activities of gemifloxacin, gatifloxacin, moxifloxacin, levofloxacin, ciprofloxacin, and other commonly used antimicrobial agents against 1,689 bacterial strains isolated at four Korean university hospitals during 1999-2000. Minimum inhibitory concentrations (MICs) were determined using the agar dilution method of National Committee for Clinical Laboratory Standards. Gemifloxacin had the lowest MICs for the respiratory pathogens: 90% of \textit{Streptococcus pneumoniae}, \textit{Moraxella catarrhalis}, and \textit{Haemophilus influenzae} were inhibited by 0.06, 0.03, and 0.03 mg/L, respectively. Gemifloxacin was more active than the other fluoroquinolones against methicillin-susceptible \textit{Staphylococcus aureus}, coagulase-negative staphylococci, streptococci, and \textit{Enterococcus faecalis}. The MICs of gemifloxacin for \textit{Klebsiella oxytoca}, \textit{Proteus vulgaris}, and non-typhoidal \textit{Salmonella} spp. were 0.25, 1.0, and 0.12 mg/L, respectively, while those for other Gram-negative bacilli were 4-64 mg/L. In conclusion, gemifloxacin was the most active among the comparative agents against Gram-positive species, including respiratory pathogens isolated in Korea.

**Key Words:** Fluoroquinolone; Gemifloxacin; Korea; \textit{Streptococcus pneumoniae}; \textit{Haemophilus influenzae}

**INTRODUCTION**

In the face of the increasing worldwide problem of antimicrobial resistance, many classes of antimicrobial agents have become less useful for therapy (1). Fluoroquinolones continued to be used for the treatment of various infections, because they are active against both Gram-positive, and Gram-negative bacteria (2-4). However, resistance to the second-generation fluoroquinolones has increased against many bacterial species. Gemifloxacin is a new fluoroquinolone under development with enhanced affinity for topoisomerase IV, and DNA gyrase, and has the lowest minimum inhibitory concentrations (MICs) against clinical isolates of \textit{Streptococcus pneumoniae} (5-7). In Korea, resistant bacteria are relatively more prevalent than in other industrialized countries, and are a serious problem currently (8). In this study, we tested the in vitro activity of gemifloxacin, and comparative agents against recent Korean bacterial isolates.

**MATERIALS AND METHODS**

A total of 1,689 clinical bacterial isolates were collected from four Korean university hospitals during 1999-2000. \textit{Neisseria gonorrhoeae} isolates were obtained, mostly from female patients. Identifications of species were performed by conventional methods or through the usage of commercial kits. MICs of gemifloxacin and other fluoroquinolones against \textit{Klebsiella oxytoca}, \textit{Proteus vulgaris}, \textit{Salmonella} spp., \textit{Staphylococcus aureus}, \textit{Haemophilus influenzae}, and \textit{Methicillin-resistant Staphylococcus aureus} (MRSA) were determined using the agar dilution method of National Committee for Clinical Laboratory Standards (NCCLS) agar dilution method (9) with Mueller-Hinton agar (BBL, Cockeysville, MD, U.S.A.), except for \textit{streptococci}, \textit{N. gonorrhoeae}, and \textit{Haemophilus influenzae}, for which 5% lysed sheep blood-supplemented Mueller-Hinton agar, IsoVitaleX (BBL)-supplemented GC agar, and \textit{Haemophilus} Test Medium, respectively, were used. The antimicrobial agents used were: gemifloxacin (LGCI, Seoul, Korea), gatifloxacin (Bristol-Myers Squibb, Princeton, New Jersey, U.S.A.), moxifloxacin (AstraZeneca, Chalfont St. Giles, U.K.), levofloxacin (Pharmacia & Upjohn, Skokie, IL, U.S.A.), and ciprofloxacin (Janssen Research Foundation, Spring House, PA, U.S.A.).\n
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Table 1. In vitro activity of gemifloxacin, and other antimicrobial agents against recent clinical isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis

| Organism (no. of isolates tested), and antimicrobial agent | MIC (mg/L) | 50% | 90% |
|----------------------------------------------------------|------------|-----|-----|
| Streptococcus pneumoniae, all (103)                      |            |     |     |
| Gemifloxacin                                             | 0.015-2    | 0.03| 0.06|
| Moxifloxacin                                             | 0.12-8     | 0.25| 0.25|
| Gatifloxacin                                             | 0.03-8     | 0.5 | 0.5 |
| Levofloxacin                                             | 0.5-32     | 1   | 2   |
| Ciprofloxacin                                            | 0.5-64     | 2   | 4   |
| Penicillin                                               | ≤0.008-8   | 2   | 4   |
| Ceftriaxone                                              | 0.015-4    | 1   | 2   |
|ERYTHROMYCIN                                              | 0.03->128  | 128 | >128|
| S. pneumoniae, Penicillin susceptible (9)                |            |     |     |
| Gemifloxacin                                             | 0.03-0.06  | 0.03|     |
| Moxifloxacin                                             | 0.12-0.25  | 0.25|     |
| Gatifloxacin                                             | 0.5        |     |     |
| Levofloxacin                                             | 1-2        |     |     |
| Ciprofloxacin                                            | 1-4        |     |     |
| Penicillin                                               | ≤0.008-0.06| 0.015|     |
| Ceftriaxone                                              | 0.015-1    | 0.03|     |
|ERYTHROMYCIN                                              | 0.03->128  | 0.06|     |
| S. pneumoniae, Penicillin intermediate (16)              |            |     |     |
| Gemifloxacin                                             | 0.015-0.12 | 0.03| 0.06|
| Moxifloxacin                                             | 0.12-0.25  | 0.25| 0.25|
| Gatifloxacin                                             | 0.06-0.5   | 0.25| 0.5 |
| Levofloxacin                                             | 1-2        | 1   | 2   |
| Ciprofloxacin                                            | 0.5-4      | 1   | 4   |
| Penicillin                                               | 0.12-1     | 0.5 | 1   |
| Ceftriaxone                                              | 0.015-4    | 0.25| 1   |
|ERYTHROMYCIN                                              | 0.03->128  | 64  | >128|
| S. pneumoniae, Penicillin resistant (78)                 |            |     |     |
| Gemifloxacin                                             | 0.015-2    | 0.03| 0.06|
| Moxifloxacin                                             | 0.12-8     | 0.25| 0.25|
| Gatifloxacin                                             | 0.03-8     | 0.5 | 0.5 |
| Levofloxacin                                             | 0.5-32     | 1   | 2   |
| Ciprofloxacin                                            | 1-64       | 2   | 4   |
| Penicillin                                               | 2-8        | 4   | 4   |
| Ceftriaxone                                              | 0.12-4     | 1   | 2   |
|ERYTHROMYCIN                                              | 0.03->128  | 128 | >128|
| Haemophilus influenzae, all (73)                         |            |     |     |
| Gemifloxacin                                             | ≤0.008-0.12|     |     |

RESULTS AND DISCUSSION

The activities of gemifloxacin, and the other antimicrobial agents against common respiratory pathogens are shown in Table 1. All isolates of S. pneumoniae, except one, were inhibited by ≤0.25 mg/L of gemifloxacin. One S. pneumoniae isolate with a gemifloxacin MIC of 2 mg/L was inhibited by 32 mg/L of levofloxacin, 64 mg/L of ciprofloxacin, 8 mg/L of moxi-
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Floxacin, and 8 mg/L of gatifloxacin. Gemifloxacin (MIC<sub>90</sub> 0.06 mg/L) was 4 to 64-fold more potent than the other quinolones (MIC<sub>90</sub> 0.25-4 mg/L), and ≥ 32-fold more potent than the non-quinolone comparators (MIC<sub>90</sub> 2->128 mg/L) for <i>S. pneumoniae</i>. The percentage of strains with a ciprofloxacin MICs of ≥ 4 mg/L was 14%, and those with a levofloxacin MICs of ≥ 8 mg/L was 1.5%. These results indicate that the resistance rates were higher than in the United States (11), and in Japan (12).

Ninety-one percent of <i>S. pneumoniae</i> (94/103) were penicillin non-susceptible, but 90% of the isolates were inhibited by ≤ 0.06 mg/L of gemifloxacin. These results were similar to those from other reports (6, 7), although two studies from North America showed a statistically significant association between resistance to penicillin, and fluoroquinolone (13, 14).

In this study, the rates of -lactamase-producing <i>H. influenzae</i>, and <i>Moraxella catarrhalis</i> were found to be higher than those reported in other countries, 66%, and 95%, respectively.

### Table 2. In vitro activity of gemifloxacin, and other antimicrobial agents against other Gram-positive aerobes

| Organism (no. of isolates tested), and antimicrobial agent | MIC (mg/L) Range | 50% | 90% |
|-----------------------------------------------------------|-----------------|-----|-----|
| Methicillin-susceptible <i>Staphylococcus aureus</i> (86)  |                 |     |     |
| Gemifloxacin                                              | 0.015-0.5       | 0.06 | 0.12|
| Moxifloxacin                                              | 0.03-32         | 0.12 | 0.25|
| Gatifloxacin                                              | 0.03-4          | 0.12 | 0.25|
| Levofloxacin                                              | 0.015-4         | 0.25 | 0.5 |
| Gatifloxacin                                              | 1-32            | 0.5  | 1   |
| Oxacillin                                                 | ≤ 0.12-2        | 0.5  | 1   |
| Erythromycin                                              | ≤ 0.12->128     | 0.5  | >128|
| Gentamicin                                                | ≤ 0.12->128     | 1    | 64  |
| Vancomycin                                                | ≤ 0.12-2        | 1    | 1   |
| Methicillin-resistant <i>S. aureus</i> (88)               |                 |     |     |
| Gemifloxacin                                              | 0.03->128       | 4    | >128|
| Moxifloxacin                                              | 0.015->128      | 16   | 128 |
| Gatifloxacin                                              | 0.06->128       | 8    | >128|
| Levofloxacin                                              | 0.25->128       | 32   | >128|
| Ciprofloxacin                                             | 0.25->128       | 64   | >128|
| Oxacillin                                                 | 4->128          | >128 | >128|
| Erythromycin                                              | 0.25->128       | >128 | >128|
| Gentamicin                                                | ≤ 0.12-128      | 1    | 2   |
| Vancomycin                                                | ≤ 0.12-2        | 1    | 2   |
| Methicillin-susceptible coagulase-negative <i>staphylococci</i> (60) | | | |
| Gemifloxacin                                              | ≤ 0.008-1       | 0.03 | 0.12|
| Moxifloxacin                                              | 0.015-4         | 0.12 | 0.25|
| Gatifloxacin                                              | 0.015-4         | 0.12 | 0.25|
| Levofloxacin                                              | 0.03-8          | 0.25 | 0.25|
| Ciprofloxacin                                             | 0.015-8         | 0.25 | 0.5 |
| Oxacillin                                                 | ≤ 0.12-0.25     | 0.25 | 0.25|
| Erythromycin                                              | ≤ 0.12->128     | 0.25 | >128|
| Gentamicin                                                | ≤ 0.12-128      | 0.5  | 16  |
| Vancomycin                                                | ≤ 0.12-2        | 1    | 2   |
| Methicillin-resistant coagulase-negative <i>staphylococci</i> (63) | | | |
| Gemifloxacin                                              | ≤ 0.008-8       | 0.12 | 1   |
| Moxifloxacin                                              | 0.015-8         | 0.25 | 4   |
| Gatifloxacin                                              | 0.03-8          | 0.25 | 4   |
| Levofloxacin                                              | 0.12-32         | 0.25 | 8   |
| Ciprofloxacin                                             | 0.015->128      | 0.25 | 128 |
| Oxacillin                                                 | 0.5->128        | 4    | 128 |
| Erythromycin                                              | ≤ 0.12->128     | 64   | >128|
| Gentamicin                                                | 0.25->128       | 64   | >128|
| Vancomycin                                                | ≤ 0.12-2        | 1    | 2   |
| <i>Enterococcus faecalis</i> (78)                         |                 |     |     |
| Gemifloxacin                                              | ≤ 0.008-8       | 0.25 | 8   |
| Moxifloxacin                                              | 0.06-32         | 0.5  | 16  |

Ninety-one percent of <i>S. pneumoniae</i> (94/103) were penicillin non-susceptible, but 90% of the isolates were inhibited by ≤ 0.06 mg/L of gemifloxacin. These results were similar to those from other reports (6, 7), although two studies from North America showed a statistically significant association between resistance to penicillin, and fluoroquinolone (13, 14).

In this study, the rates of β-lactamase-producing <i>H. influenzae</i>, and <i>Moraxella catarrhalis</i> were found to be higher than those reported in other countries, 66%, and 95%, respectively.
Table 3. In vitro activity of gemifloxacin, and other antimicrobial agents against Enterobacteriaceae, glucose-nonfermenters, and Neisseria gonorrhoeae (Table 3. Continued next)

| Organism (no. of isolates tested), and antimicrobial agent | MIC (mg/L) | Organism (no. of isolates tested), and antimicrobial agent | MIC (mg/L) |
|-----------------------------------------------------------|------------|-----------------------------------------------------------|------------|
| Escherichia coli (81)                                     |            |                                                          |            |
| Gemifloxacin                                               | ≤ 0.008-128| 0.12 64                                                   |            |
| Moxifloxacin                                               | ≤ 0.008-128| 0.25 64                                                   |            |
| Gatifloxacin                                               | ≤ 0.008-64 | 0.06 8                                                    |            |
| Levofloxacin                                               | ≤ 0.008-128| 0.25 16                                                   |            |
| Ciprofloxacin                                              | ≤ 0.008-128| 0.12 >128                                                 |            |
| Ampicillin                                                 | 2-128 >128 | >128 >128                                                 |            |
| Cefuroxime                                                 | 1-128 4    | 32                                                        |            |
| Ceftriaxone                                                | ≤ 0.008-128| 0.06 16                                                   |            |
| Imipenem                                                   | 0.03-1     | 0.25 0.25                                                 |            |
| Amoxicillin-clavulanic acid                               | 2-128 32   | 64                                                        |            |
| Gentamicin                                                 | 0.25-128 1 | >128 >128                                                 |            |
| Klebsiella pneumoniae (81)                                 |            |                                                          |            |
| Gemifloxacin                                               | 0.03-128   | 0.06 4                                                    |            |
| Moxifloxacin                                               | 0.06-128   | 0.25 4                                                    |            |
| Gatifloxacin                                               | 0.015-128  | 0.06 2                                                    |            |
| Levofloxacin                                               | 0.03-128   | 0.06 4                                                    |            |
| Ciprofloxacin                                              | ≤ 0.008-128| 0.03 2                                                    |            |
| Ampicillin                                                 | 4-128 >128 | >128 >128                                                 |            |
| Cefuroxime                                                 | 0.5-128 4  | >128 >128                                                 |            |
| Ceftriaxone                                                | 0.015-128  | 0.06 128                                                  |            |
| Imipenem                                                   | 0.03-4     | 0.25 4                                                    |            |
| Amoxicillin-clavulanic acid                               | 0.5-128 8  | 64                                                        |            |
| Gentamicin                                                 | 0.25-128 0.5 | >128 >128                                               |            |
| Klebsiella oxytoca (55)                                    |            |                                                          |            |
| Gemifloxacin                                               | ≤ 0.008-8  | 0.06 0.25                                                 |            |
| Moxifloxacin                                               | 0.03-8     | 0.12 1                                                    |            |
| Gatifloxacin                                               | 0.015-2    | 0.06 0.12                                                 |            |
| Levofloxacin                                               | 0.03-2     | 0.06 0.12                                                 |            |
| Ciprofloxacin                                              | ≤ 0.008-2  | 0.015 0.06                                                |            |
| Ampicillin                                                 | 32-128 64  | >128 >128                                                 |            |
| Cefuroxime                                                 | 1-128 4    | 64                                                        |            |
| Ceftriaxone                                                | 0.03-128   | 0.12 32                                                   |            |
| Imipenem                                                   | 0.12-1     | 0.25 0.5                                                  |            |
| Amoxicillin-clavulanic acid                               | 1-128 8    | 32                                                        |            |
| Gentamicin                                                 | 0.25-128 0.5 | >128 >128                                               |            |
| Proteus vulgaris (42)                                      |            |                                                          |            |
| Gemifloxacin                                               | 0.015-16   | 0.25 1                                                    |            |
| Moxifloxacin                                               | 0.12-16    | 0.5 4                                                     |            |
| Gatifloxacin                                               | 0.015-2    | 0.12 0.5                                                  |            |
| Levofloxacin                                               | 0.015-1    | 0.06 0.25                                                 |            |
| Ciprofloxacin                                              | 0.015-1    | 0.03 0.25                                                 |            |
| Ampicillin                                                 | 2-128 >128 | >128 >128                                                 |            |
| Cefuroxime                                                 | 1-128 >128 | >128 >128                                                 |            |
| Ceftriaxone                                                | ≤ 0.008-4  | 0.12 1                                                    |            |
| Imipenem                                                   | 0.03-8     | 2 4                                                       |            |
| Amoxicillin-clavulanic acid                               | 0.12-128 8 | 64                                                        |            |
| Gentamicin                                                 | 0.25-16 0.5 | >128 >128                                               |            |
| P. mirabilis (63)                                          |            |                                                          |            |
| Gemifloxacin                                               | 0.03-16    | 0.25 8                                                    |            |
| Moxifloxacin                                               | 0.06-64    | 1 8                                                       |            |
| Gatifloxacin                                               | 0.03-16    | 0.25 2                                                    |            |
| Levofloxacin                                               | 0.03-8     | 0.12 2                                                    |            |
| Ciprofloxacin                                              | 0.015-4    | 0.06 1                                                    |            |
| Ampicillin                                                 | 1-128 128  | >128 >128                                                 |            |

(Continued next page)
Table 3. (Continued from the previous page) In vitro activity of gemifloxacin, and other antimicrobial agents against Enterobacteriaceae, glucose-nonfermenters, and Neisseria gonorrhoeae

| Organism (no. of isolates tested), and antimicrobial agent | MIC (mg/L) | Range | 50% | 90% |
|----------------------------------------------------------|------------|-------|-----|-----|
| *Serratia marcescens* (61)                                |            |       |     |     |
| Gemifloxacin                                              | 0.03-128   | 2     | 16  |     |
| Moxifloxacin                                              | 0.12-128   | 1     | 32  |     |
| Gentamicin                                                | 0.25-128   | 8     | 128 |     |
| Amoxicillin-clavulanic acid                               | 0.25-128   | 64    | >128|     |
| Ceftriaxone                                               | ≤0.008-128 | 0.03  | 0.5 |     |
| Cefuroxime                                                | ≤0.06-128  | 2     | 64  |     |
| Imipenem                                                  | 0.5-8      | 1     | 4   |     |
| Gentamicin                                                | 0.25-128   | 8     | 128 |     |
| Amoxicillin-clavulanic acid                               | 0.25-128   | 16    | >128|     |
| *Pseudomonas aeruginosa* (83)                             |            |       |     |     |
| Gemifloxacin                                              | 0.25-128   | 4     | 128 |     |
| Moxifloxacin                                              | 0.5-128    | 16    | >128|     |
| Gentamicin                                                | 0.25-128   | 2     | 16  |     |
| Ceftriaxone                                               | >128       | >128  |     |     |
| Gentamicin                                                | 1-128      | 16    | >128|     |
| *Acinetobacter baumannii* (84)                            |            |       |     |     |
| Gemifloxacin                                              | 0.015-64   | 8     | 64  |     |
| Ceftriaxone                                               | 0.25-128   | 8     | >128|     |
| Gentamicin                                                | 0.5-128    | 2     | 16  |     |

(15). Although all of the isolates were inhibited by ≤1 mg/L of all of the fluoroquinolones tested, gemifloxacin had the lowest MIC<sub>90</sub> and MIC<sub>50</sub>, regardless of β-lactamase production. This finding is consistent with other reports (5-7, 16, 17).

The MIC<sub>90</sub> of gemifloxacin for methicillin-susceptible *S. aureus* (MSSA), and methicillin-susceptible, and -resistant coagulase-negative staphylococci were 0.12, 0.12, and 1 mg/L, respectively (Table 2). In the present study, gemifloxacin was 2 to 128-fold more potent than the other quinolones (MIC<sub>90</sub> 0.25-128 mg/L), and 2 to >128-fold more potent than the non-quinolone comparators (MIC<sub>90</sub> 0.25-128 mg/L) for these isolates. Most of the methicillin-resistant *S. aureus* (MRSA) isolates were less susceptible than MSSA to all of the fluoroquinolones.

None of the *E. faecalis* isolates in this study were resistant to vancomycin, while 20% of the *Enterococcus faecium* isolates were vancomycin resistant (Table 2). The MIC<sub>90</sub> (0.25 mg/L), and MIC<sub>50</sub> (8 mg/L) of gemifloxacin were 2 to 8-fold lower than the other quinolones for *E. faecalis*. Gemifloxacin was the most potent of the fluoroquinolones studied against *E. faecalis*; however, strains with reduced gemifloxacin susceptibilities were noted, particularly in *E. faecium*. For streptococci other than *S. pneumoniae*, the MIC<sub>90</sub> of gemifloxacin was 0.25 mg/L, which was 1- to 16-fold lower than that of the other quinolones.

The in vitro activity of fluoroquinolones against Gram-negative bacilli was found to vary significantly, depending on species. In general, the MICs of ciprofloxacin were lower than those of the other quinolones for Gram-negative bacilli, except for *E. coli*, Providencia spp., *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. The MIC<sub>90</sub> of gemifloxacin for *K. oxytoca*, *Proteus vulgaris*, and non-typhoidal Salmonella were 0.25, 1.0, and 0.12 mg/L, respectively, while those for other Enterobacteriaceae were 4-64 mg/L, which were similar to or slightly higher than those of ciprofloxacin (Table 3). None of the *N. gonorrhoeae* isolates tested were susceptible to penicillin. The MIC<sub>90</sub> of ciprofloxacin was 0.5 mg/L, and 92% of *N. gonorrhoeae* were non-susceptible to ciprofloxacin. This rate was higher than that of other reports. Ciprofloxacin-non-sus-
ceptible N. gonorrhoeae also showed reduced susceptibility to other fluoroquinolones, but the MIC_{50} of gemifloxacin, and gatifloxacin were 4-fold lower than that of ciprofloxacin.

The quinolones are absorbed quickly, attaining maximum plasma concentration within 1-2 hr of oral administration. The maximum plasma concentrations (bronchial mucosa: plasma ratios) were 1.2 mg/L (7.2), 1.2 mg/L (2.1), 3.9 mg/L (1.7), 5.1 mg/L (1.6), and 2.3 mg/L (1.7) with a single oral administration of 520 mg gemifloxacin, 200 mg moxifloxacin, 400 mg gatifloxacin, 500 mg levofloxacin, and 500 mg ciprofloxacin, respectively (18, unpublished data). Therefore, it was considered those concentrations of fluoroquinolones in bronchial mucosa were 8.6, 2.5, 6.6, 8.2, 3.9 mg/L, respectively.

In conclusion, gemifloxacin was most active in vitro against Gram-positive species, including respiratory pathogens isolated in Korea. Therefore, gemifloxacin should be useful for the treatment of the majority of respiratory, and other infections, especially those due to Gram-positive cocci.

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