Activity of Respiratory Fluoroquinolones Gemifloxacin (GEM), Moxifloxacin (MOX), Gatifloxacin (GAT) and Levofloxacin (LEV) Against 4982 Upper and Lower Respiratory Tract *Streptococcus pneumoniae* (*SP*) Isolates Recovered From 124 Sites in the United States: The FACTS Study, 2000–2001

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Revised Abstract

Background: *SP* continues to exhibit high levels of resistance to penicillin (PEN) and macrolides. Fluoroquinolones are increasingly being used as alternative therapy in the treatment of this pathogen. Investigations of fluoroquinolone activity have reported MIC_{90}s of 0.03, 0.25, 0.5 and1.0 µg/ml for GEM, MOX, GAT and LEV, respectively, against *SP* respiratory isolates. The objective of this study was to determine the activity of respiratory fluoroquinolones against lower respiratory tract infections (LRTIs) caused by *SP* in comparison with *SP* found in upper respiratory tract (eyes, ears, nose and throat) infections (URTIs). **Method:** Susceptibility determinations were performed on 4892 *SP* isolates from URTIs (n = 594) and LRTIs (n = 4298) in a two-phase study. The first phase measured PEN, erythromycin (ERY), clindamycin (CC), and GEM and LEV activity by disk diffusion and/or Etest methodology. Isolates with a MIC of ≥1.5 µg/ml to LEV (indicating possible mutation[s]) were tested in phase II against GEM, MOX, GAT and LEV using the Etest methodology. Interpretations were made based on NCCLS guidelines (analysis for GEM was based on susceptible, intermediate and resistant breakpoints of ≤0.25, 0.5 and ≥1.0 µg/ml, respectively). **Results:** In phase 1, the level of resistant *SP* isolates in URTIs for GEM and LEV were 0.5% and 1.7%, respectively. In LRTIs, resistance was measured at 0.2% and 0.9% for GEM and LEV, respectively. PEN, CC and ERY resistances were 18.7%, 12.6% and 30.0%, and 17.5%, 9.8% and 28.4%, for URTI and LRTI isolates, respectively. In isolates with a LEV MIC of ≥1.5 µg/ml, resistances in URTI/LRTI *SP* were higher for LEV (25.6%/13.3%), GAT (20.5%/10.5%) and MOX (17.9%/8.4%) and lowest for GEM (7.7%/2.8%). **Conclusion:** All fluoroquinolones tested exhibited good activity against both upper and lower *SP* isolates, with GEM exhibiting the lowest percentage resistances against this pathogen. *SP* isolates from URTIs with LEV MICs of ≥1.5 µg/ml exhibit slightly higher resistances to all fluoroquinolones than isolates found in LRTIs.

Introduction

With penicillin and macrolide non-susceptible rates for *Streptococcus pneumoniae* increasing dramatically in the past decade in the USA[1] and other countries, many clinicians are turning to quinolones as first-line therapy for respiratory tract infections. However, large surveillance studies are needed to monitor what resistance rates exist, if any, among the newer quinolones, especially the respiratory quinolones, being developed and introduced against this important pathogen.

Objectives

Approximately 7319 isolates of *S. pneumoniae* from the USA and Canada were evaluated in the FACTS study. Primary screening was performed to determine the current susceptibility and resistance of *S. pneumoniae* to penicillin, macrolides and quinolones. Further testing was performed on *S. pneumoniae* isolates with levofloxacin MICs of ≥1.5 µg/ml with a battery of fluoroquinolones.

Materials and Methods

- Isolates were collected between January 1, 2000, and December 31, 2001, from 124 geographically distributed centers in the USA and one in Canada.
- Each center was required to collect a total of 75 clinically significant isolates of *S. pneumoniae*.
- All isolates were derived from patients ≥16 years of age and were clinical specimens of the upper and lower respiratory tract, nasopharynx, sputum and blood. Only one isolate per patient was accepted.
- Organism collection, transport, confirmation of organism identification, as well as construction and management of a centralized database, were coordinated by International Health Management Associates, Inc. (Rolling Meadows, IL, USA).

Antimicrobial Susceptibility Testing

- Each isolate of *S. pneumoniae* was tested in phase I.
- Phase I: primary screening was performed against erythromycin, clindamycin, gemifloxacin and levofloxacin by disk diffusion. Each isolate was also tested against penicillin, gemifloxacin and levofloxacin by the concentration gradient agar diffusion method (Etest).
- Phase II: a panel of quinolones was tested against any isolate from phase I that had a levofloxacin Etest MIC value of ≥1.5 µg/ml and/or gemifloxacin zone of ≤15 mm or Etest MIC value of ≥0.25 µg/ml. Phase II included testing against gemifloxacin, moxifloxacin, gatifloxacin and levofloxacin by Etest methodology.
- Etest methodology followed manufacturer's guidelines (AB Biodisk, Solna, Sweden). Disk diffusion methodology proceeded according to NCCLS[2] and manufacturer's guidelines (Becton-Dickinson, Sparks, MD, USA).
- Quality control of Etest and antimicrobial disks were performed following NCCLS[2] and manufacturer's guidelines.

Results

Results of the study are listed in Tables 1–3.

Table 1. Location, Source and Distribution (n) of Respiratory Specimens

Location	Source	n	% of total
Upper respiratory (n = 594)	Eye	170	3.5
	Ear	77	1.6
	Nose	98	2.0
	Throat	77	1.6
	Sinus	172	3.5
Lower respiratory (n = 4298)	Lung	36	0.7
	Trachea	252	5.2
	Bronchi	295	6.0
	Sputum	3715	75.9
Total		4892	100

Table 2. Phase I *In Vitro* Activity and Susceptibility of Gemifloxacin and Comparators Against 4892 Upper and Lower Respiratory *S. pneumoniae* Isolates

Source	Drug	$MIC_{50/90}$ (µg/ml)	%S	%I	%R
All sources (n = 4892)	Gemifloxacin[a]	0.032/0.047	99.4	0.4	0.2
	Levofloxacin	0.75/1	98.8	0.2	1.0
	Penicillin[b]	–	62.4	19.9	17.7
	Erythromycin[b]	–	69.8	1.6	28.6
	Clindamycin[b]	–	88.4	1.4	10.2
Upper respiratory (n = 594)	Gemifloxacin[a]	0.023/0.047	99.0	0.5	0.5
	Levofloxacin	0.75/1	98.0	0.3	1.7
	Penicillin[b]	–	63.8	17.5	18.7
	Erythromycin[b]	–	68.9	1.1	30.0
	Clindamycin[b]	–	86.5	0.9	12.6
Lower respiratory (n = 4298)	Gemifloxacin[a]	0.032/0.047	99.5	0.3	0.2
	Levofloxacin	0.75/1	99.0	0.1	0.9
	Penicillin[b]	–	62.3	20.2	17.5
	Erythromycin[b]	–	69.9	1.7	28.4
	Clindamycin[b]	–	88.7	1.5	9.8

%S, percentage susceptible; %I, percentage intermediate; %R, percentage resistant
[a]Analysis for gemifloxacin was based on susceptible, intermediate and resistant breakpoints of ≤0.25, 0.5 and ≥1.0 µg/ml, respectively
[b]Disk diffusion

Table 3. Phase II *In Vitro* Activity and Susceptibility of Gemifloxacin and Comparators Against 324 (6.6%) Upper and Lower Respiratory *S. pneumoniae* Isolates with Levofloxacin MICs ≥ 1.5 µg/ml

Source	Drug	$MIC_{50/90}$ (µg/ml)	%S	%I	%R
All sources (n = 324)	Gemifloxacin[a]	0.064/0.25	91.7	4.9	3.4
	Moxifloxacin	0.25/2	86.7	3.7	9.6
	Gatifloxacin	0.5/4	86.1	2.2	11.7
	Levofloxacin	1.5/>32	82.4	2.8	14.8
Upper respiratory (n = 39)	Gemifloxacin[a]	0.064/0.5	84.6	7.7	7.7
	Moxifloxacin	0.25/6	76.9	5.2	17.9
	Gatifloxacin	0.38/16	76.9	2.6	20.5
	Levofloxacin	1.5/>32	69.2	5.2	25.6
Lower respiratory (n = 285)	Gemifloxacin[a]	0.064/0.19	92.6	4.6	2.8
	Moxifloxacin	0.25/2	88.1	3.5	8.4
	Gatifloxacin	0.5/3	87.4	2.1	10.5
	Levofloxacin	1.5/>32	84.2	2.5	13.3

%S, percentage susceptible; %I, percentage intermediate; %R, percentage resistant
[a]Analysis for gemifloxacin was based on susceptible, intermediate and resistant breakpoints of ≤0.25, 0.5 and ≥1.0 µg/ml, respectively

Discussion

Since the first report of penicillin-resistant *S. pneumoniae* in 1965, the concentration of penicillin required to inhibit or kill this pathogen has increased. Today, with the incidence of penicillin-resistant and macrolide-resistant isolates of *S. pneumoniae* approaching parity with susceptible isolates, quinolones are being used more frequently in empirical therapy for respiratory tract infections. However, the quinolones are not immune to resistance problems with respect to *S. pneumoniae*. Although the incidence of quinolone resistance in *S. pneumoniae* is relatively low to date, increasing prevalence of these isolates could potentially restrict the empirical use of this class of drugs in the treatment of respiratory infections.

Surveillance studies have documented a gradual increase in ciprofloxacin MICs to *S. pneumoniae* over the past decade.[3–7] Recent studies place the incidence of ciprofloxacin-resistant *S. pneumoniae* (ciprofloxacin MICs ≥ 4 µg/ml) at 0.03% (17/5640) in the USA[1] and as high as 3.0% (22/727) in Spain.[8] We found the incidence of levofloxacin-resistant *S. pneumoniae* in this study to be 0.8%, which is higher than 0.3–0.6% found in other studies[5,9,10] but is still below 1%.

Newer extended-spectrum quinolones such as gemifloxacin, moxifloxacin and gatifloxacin represent compounds of this antimicrobial class with enhanced Gram positive activity over that of ciprofloxacin and levofloxacin. We examined 4892 upper and lower respiratory isolates of *S. pneumoniae* from the USA and Canada in order to determine what resistance, if any, is present in these new drugs.

We found gemifloxacin to be the most active oral agent in this study, with an *in vitro* MIC_{90} of 0.047 µg/ml against all specimens compared with a MIC_{90} of 1 µg/ml for levofloxacin. Gemifloxacin also had the lowest resistance rate (0.2%) compared with levofloxacin (1.0%), penicillin (17.7%) and erythromycin (28.6%). Resistance rates were relatively unchanged for penicillin, clindamycin and erythromycin regardless of specimen location, upper or lower respiratory tract. However, there was a 2-fold difference in resistance rates for both gemifloxacin (0.2% to 0.5%) and levofloxacin (0.9% to 1.7%) among isolates from lower respiratory tract specimens and upper respiratory tract specimens ($p < 0.005$).

Gemifloxacin had the lowest MICs of all the study quinolones among isolates with possible first- and second-step mutations (levofloxacin MICs ≥1.5 µg/ml) with a MIC_{90} of 0.25 µg/ml compared with >32 µg/ml for levofloxacin, 4 µg/ml for gatifloxacin and 2 µg/ml for moxifloxacin. Resistance rates in upper respiratory tract isolates were approximately double the resistance rates of those from lower respiratory tract sources ($p < 0.005$) for the four study quinolones.

Overall, gemifloxacin had the highest susceptibility, lowest MICs and lowest percentage resistance of all the newer quinolones tested against *S. pneumoniae* regardless of respiratory source.

Conclusions

- Quinolones exhibited excellent activity against all isolates of *S. pneumoniae* from respiratory sources taken from study centers in the USA and Canada.
- The quinolone resistance rate (levofloxacin MIC ≥8 µg/ml) was 1% for respiratory isolates of *S. pneumoniae* from study centers in the USA and Canada.
- The gemifloxacin MIC_{90} of 0.047 µg/ml was 16-fold lower than that of levofloxacin against all *S. pneumoniae* isolates from respiratory sources.
- The gemifloxacin MIC_{90} of 0.25 µg/ml was 8- to 16-fold lower than that of moxifloxacin and gatifloxacin, respectively, against all *S. pneumoniae* isolates with possible quinolone-resistant mutations (levofloxacin MICs ≥1.5 µg/ml).
- Quinolone *in vitro* resistance rates approximately doubled for upper respiratory *versus* lower respiratory isolates.

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