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Antimicrobial activity and a comparison of published pharmacodynamics of gemifloxacin and eight fluoroquinolones against *Streptococcus pneumoniae*

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Abstract

Gemifloxacin was evaluated for its in vitro activity and was compared with eight fluoroquinolones. Pharmacodynamic comparisons were made based on published pharmacokinetic information. Gemifloxacin demonstrated excellent in vitro activity (minimum inhibitory concentration necessary to inhibit 90% of the strains tested, MIC_{90} = 0.03 mg/L (range 0.0019–0.03 mg/L)) against 199 strains of *Streptococcus pneumoniae*. Its activity was not influenced by penicillin or ciprofloxacin non-susceptibility. Gemifloxacin demonstrated excellent pharmacodynamic parameters, with a C_{max}/MIC_{90} of 67 (where C_{max} is the peak serum level) and an AUC/MIC_{90} of 297 (where AUC is the area under the curve). Compared with the other eight fluoroquinolones tested, gemifloxacin demonstrated the best in vitro activity and C_{max}/MIC_{90}.

Keywords: Gemifloxacin; Fluoroquinolones; *Streptococcus pneumoniae*; In vitro

1. Introduction

Gemifloxacin is a new respiratory tract fluoroquinolone developed with enhanced potency against *Streptococcus pneumoniae* and other respiratory tract pathogens [1,2]. Because of the enhanced activity of several recently released fluoroquinolones against Gram-positive bacteria, along with the increasing incidence of penicillin non-susceptible strains of *S. pneumoniae*, this study was undertaken to compare the in vitro activity of gemifloxacin with the activity of eight other fluoroquinolones. Since pharmacodynamics have become an important feature in the assessment of activity of fluoroquinolones against Gram-positive respiratory pathogens, we evaluated pharmacodynamic profiles of all the fluoroquinolones studied based on published pharmacokinetic profiles. This study provided information on gemifloxacin and eight other fluoroquinolones regarding microbiological and pharmacodynamic activity.

2. Materials and methods

2.1. Bacterial strains

S. pneumoniae strains (N = 199) isolated from a ten hospital healthcare system in Michigan were collected from clinical specimens and stored at −70 °C. Only one isolate per patient was included, thus excluding duplication. The isolates were collected from blood (66), respiratory secretions (132) and cerebrospinal fluid (1).

2.2. Antimicrobial agents

Antimicrobial agents as standard powders were provided by the manufacturer and included: gemifloxacin (SmithKline Beecham, Collegenable, PA), gatifloxacin (Bristol-Myers Squibb, Princeton, NJ), ciprofloxacin, moxifloxacin (Bayer Corp., West Haven, CT), clinafloxacin, sparfloxacin (Parke Davis, Ann Arbor, MI), grepafloxacin (Glaxo-Wellcome, Research Triangle Park, NC), levofloxacin (Ortho-McNeil, Raritan, NJ) and trovafloxacin (Pfizer, Groton, CT). The pow-

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Table 1
Susceptibility of 199 *Streptococcus pneumoniae* clinical isolates and pharmacodynamics for gemifloxacin and the eight other fluoroquinolones tested[a]

Antimicrobial agent	MIC (mg/L)			Dose	C_{max} (mg/L)	C_{max}/MIC_{90}	AUC (mg·h/L)	PB (%)	AUC/MIC_{90}
	Range	MIC_{50}	MIC_{90}						
Gemifloxacin	0.0019–0.03	0.0015	0.03	320 mg po	2.0	67	8.91	57	297
Moxifloxacin	0.03–2	0.13	0.13	400 mg po	4.5	34.6	48	30	369
Trovafloxacin	0.03–64	0.13	0.25	200 mg iv	2.2	8.8	30.4	70	122
Clinafloxacin	0.03–0.25	0.06	0.13	200 mg po	1.6	12.3	11	50	85
Gatifloxacin	0.13–1	0.50	0.50	400 mg iv	4.6	9.2	35.5	20	71
Levofloxacin	0.03–64	0.5	1.0	500 mg iv	5.2	5.2	61.1	24	61
Grepafloxacin	0.03–2	0.13	0.25	400 mg po	1.5	6.0	12	50	48
Sparfloxacin	0.03–1	0.25	0.50	400 mg po	0.6	1.2	16.4	45	33
Ciprofloxacin	0.03–8	1.0	2.0	400 mg iv	4.0	2.0	12	35	6

po, by mouth; iv, intravenous.
[a] When evaluating quinolone activity relative to penicillin susceptibility, isolates categorised as penicillin susceptible (PSSP), intermediate (PISP) and resistant (PRSP) showed no difference for any of the fluoroquinolones tested.

ders were used to prepare stock antibiotic dilutions as outlined in the National Committee for Clinical Laboratory Standards (NCCLS) [3].

2.3. Minimum inhibitory concentrations (MICs)

MICs were determined by microdilution broth assay using cation-adjusted Mueller–Hinton broth supplemented with 2–5% lysed horse blood (Cleveland Scientific, Bath, OH). Suspensions were prepared from an 18 h pure culture in saline adjusted to a 0.5 McFarland standard with a final inoculum of 5×10^5 colony-forming units (CFU)/mL. Microtitre plates were incubated at 35 °C for 18–24 h in air. The standard quality control strain *S. pneumoniae* ATCC 49619 was included in each run. Breakpoints used for penicillin susceptibility were divided into three categories according to NCCLS guidelines: penicillin susceptible (PSSP), MIC < 0.06 mg/L; intermediate (PISP), MIC = 0.12–1.0 mg/L; and resistant (PRSP), MIC > 2.0 mg/L [3].

2.4. Pharmacodynamics

Therapeutic indices were calculated by dividing published peak serum levels (C_{max}) by the appropriate MIC necessary to inhibit 90% of strains tested (MIC_{90}). AUC/MIC ratios were calculated from published pharmacokinetic data providing the area under the curve (AUC) divided by the MIC_{90} values determined in the study [4,5].

3. Results

The susceptibility data determined for each of the antimicrobial agents tested are summarised in Table 1. All isolates tested were susceptible to the fluoroquinolones apart from ciprofloxacin, where 10 isolates (5%) had a MIC at or above the breakpoint of 4 mg/L. All fluoroquinolones tested, except for ciprofloxacin and levofloxacin, had MIC_{90} < 1.0 mg/L.

Table 2 summarises the in vitro susceptibility for the ciprofloxacin non-susceptible strains of *S. pneumoniae*. The MIC_{90} for the 10 non-susceptible isolates was identical to the MIC_{90} for the 199 isolates for grepafloxacin, trovafloxacin, sparfloxacin and clinafloxacin. For levofloxacin, gatifloxacin and moxifloxacin there was a two-fold rise in MIC_{90}, suggesting an insignificant change in in vitro activity. Gemifloxacin demonstrated a four-fold lower MIC_{90} for the ciprofloxacin-non-susceptible strains compared with susceptible strains.

When evaluating quinolone activity relative to penicillin susceptibility, isolates categorised into groups as PSSP (54), PISP (78) and PRSP (67) showed no difference for any of the fluoroquinolones tested.

The in vitro activity relative to pharmacokinetics is expressed as pharmacodynamic parameters in Table 1 and Fig. 1. Looking at C_{max}/MIC_{90}, these data show the rank order of activity as gemifloxacin > moxifloxacin > clinafloxacin > gatifloxacin > trovafloxacin > grepafloxacin > levofloxacin > ciprofloxacin > sparfloxacin.

The AUC/MIC ratios suggest a slightly different rank order in terms of pharmacodynamics, with moxifloxacin > gemifloxacin > trovafloxacin > clinafloxacin > gatifloxacin > levofloxacin > grepafloxacin > sparfloxacin > ciprofloxacin. Evaluating agents in terms of free drug and total drug shows a difference in relative ranking of the fluoroquinolones tested, with moxifloxacin > gemifloxacin > gatifloxacin > levofloxacin > clinafloxacin > trovafloxacin > sparfloxacin > grepafloxacin > ciprofloxacin (Fig. 1).

Table 2
Fluoroquinolone minimum inhibitory concentrations (MICs) for the 10 isolates with reduced susceptibility to ciprofloxacin (MIC ≥ 4 mg/L)

Antimicrobial agent	Range	MIC_{90}
Gemifloxacin	0.0037–0.03	0.0075
Moxifloxacin	0.03–0.25	0.25
Trovafloxacin	0.06–0.5	0.25
Clinafloxacin	0.03–013	0.13
Gatifloxacin	0.25–1.0	1.0
Levofloxacin	0.5–2.0	2.0
Grepafloxacin	0.06–1.0	0.25
Sparfloxacin	0.13–0.5	0.5
Ciprofloxacin	4.0–8.0	8.0