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In Vitro Activity of BAY 12-8039, a Novel 8-Methoxyquinolone, Compared to Activities of Six Fluoroquinolones against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*

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The in vitro activity of a novel 8-methoxyquinolone, BAY 12-8039, against recent clinical isolates of *Streptococcus pneumoniae* ($n = 404$), *Haemophilus influenzae* ($n = 330$), and *Moraxella catarrhalis* ($n = 250$) was evaluated. Activity was compared to those of six other fluoroquinolones: ciprofloxacin, clinafloxacin, levofloxacin, ofloxacin, sparfloxacin and trovafloxacin. BAY 12-8039 and clinafloxacin had the highest levels of activity against *S. pneumoniae*, both with a MIC at which 90% of the isolates were inhibited (MIC_{90}) of 0.06 μg/ml. Trovafloxacin and sparfloxacin were the next most active agents versus *S. pneumoniae* (MIC_{90}s = 0.12 μg/ml). No differences in activity against penicillin-susceptible, -intermediate, or -resistant strains of *S. pneumoniae* were noted for any of the fluoroquinolones tested. MIC_{90}s for the seven fluoroquinolones ranged from 0.008 to 0.06 μg/ml versus *H. influenzae* and from 0.008 to 0.12 μg/ml for *M. catarrhalis*. The MICs for two strains of *S. pneumoniae* and one strain of *H. influenzae* were noted to be higher than those for the general population of organisms for all of the fluoroquinolones tested. Finally, the activity of BAY 12-8039 versus *S. pneumoniae* was found to be diminished when MIC determinations were performed with incubation of agar dilution plates or broth microdilution trays in 5 to 7% CO_2 versus ambient air.

The fluoroquinolones as a class of antibacterial agents first experienced widespread clinical use during the 1980s with the release of norfloxacin and ciprofloxacin (13). Since then, numerous additional fluoroquinolones have been developed. In general, the fluoroquinolones have proven to be effective in the management of infections due to gram-negative bacteria (1, 25). The utility of currently available agents in treating infections caused by gram-positive organisms is questionable (21). *Streptococcus pneumoniae* is of particular concern, as evidenced by reports of incomplete bacterial eradication and therapeutic failure with ciprofloxacin (5, 16, 17, 20). As penicillin resistance has emerged as a major problem with *S. pneumoniae* (2), effective, alternative non-β-lactam therapies have become necessary. In this regard, the recent development of several fluoroquinolones with extended gram-positive activity is of interest (21).

This study was undertaken to assess the in vitro activity of a novel 8-methoxyquinolone, BAY 12-8039 (1-cyclopropyl-7[(*S*,*S*)-2,8-diazabicyclo[4.3.0] non-8-yl]-6-fluoro-8-methoxy-1,4-dihydro-4-oxo-3-quinoline carboxylic acid) against *S. pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Preliminary reports describing the in vitro activity of BAY 12-8039 indicate that this new agent possesses the typical activity profile of a fluoroquinolone against gram-negative bacteria such as the *Enterobacteriaceae* and *Pseudomonas*, *Chlamydia*, and *Mycoplasma* species, in addition to having an added spectrum of gram-positive activity (10, 12, 15, 23, 24, 26). In this study, we compared the in vitro activity of BAY 12-8039 to those obtained with six other quinolones, ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, trovafloxacin, and clinafloxacin, against *S. pneumoniae*. The latter four agents were chosen because of their extended gram-positive activity (3, 4, 9). Because of the frequency with which *S. pneumoniae* is recognized as a cause of outpatient infections that are typically treated empirically, i.e., acute otitis media, maxillary sinusitis, acute purulent exacerbation of chronic bronchitis, and community-acquired pneumonia, we also assessed the activities of the fluoroquinolones against recent clinical isolates of two other bacteria that commonly cause these diseases, *H. influenzae* and *M. catarrhalis.*

MATERIALS AND METHODS

Representative isolates of *S. pneumoniae* ($n = 404$), *H. influenzae* ($n = 330$), and *M. catarrhalis* ($n = 250$) were selected from a collection of clinical isolates obtained from outpatients in 30 United States medical centers during the winter months of 1994 to 1995 as part of a national surveillance study of antimicrobial resistance (6–8). Broth microdilution as recommended by the National Committee for Clinical Laboratory Standards (18) was used to determine MICs. The following media were used: *S. pneumoniae*, cation-adjusted Mueller-Hinton broth (MHB) supplemented with 3% lysed horse blood; *H. influenzae*, haemophilus test medium (14); and *M. catarrhalis*, MHB. The following American Type Culture Collection control strains were used: *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49247, ATCC 10211, and ATCC 49766, and *Escherichia coli* ATCC 25922. Antimicrobials were obtained as laboratory grade powders from their respective manufacturers: BAY 12-8039, Bayer Corporation; ciprofloxacin, Miles Pharmaceuticals; clinafloxacin, Parke-Davis Pharmaceutical; levofloxacin and ofloxacin, Roussel Uclaf; sparfloxacin, Rhone-Poulenc Rorer; and trovafloxacin, Pfizer, Inc. Isolates were stored at −70°C by using porous beads with two subcultures made before the organisms were tested. Following inoculation (ca. 5×10^5 CFU/ml final inoculum concentration), MIC trays were incubated at 37°C in ambient air for 24 h before examination.

RESULTS

Results of MIC determinations are listed in Table 1. BAY 12-8039 and clinafloxacin, both with a MIC at which 90% of the isolates were inhibited (MIC_{90}) of 0.06 μg/ml, had the

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TABLE 1. In vitro activities of BAY 12-8039 and other fluoroquinolone antibiotics versus *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*

Organism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)			
		50%	90%	Geometric mean	Range
S. pneumoniae					
Penicillin susceptible[a] (154)	BAY 12-8039	0.03	0.06	0.04	0.015–0.06
	Clinafloxacin	0.03	0.06	0.04	0.015–0.06
	Trovafloxacin	0.12	0.12	0.09	0.03–0.25
	Sparfloxacin	0.12	0.12	0.14	0.06–0.25
	Levofloxacin	0.5	1	0.75	0.25–1
	Ciprofloxacin	0.5	1	0.74	0.25–2
	Ofloxacin	1	1	1.03	0.5–2
Penicillin intermediate[b] (150)	BAY 12-8039	0.03	0.06	0.04	≤0.004–4
	Clinafloxacin	0.03	0.06	0.04	0.015–0.5
	Trovafloxacin	0.06	0.12	0.09	≤0.004–8
	Sparfloxacin	0.12	0.12	0.15	0.06–16
	Levofloxacin	0.5	1	0.74	0.5–16
	Ciprofloxacin	1	1	0.77	0.25–>8
	Ofloxacin	1	1	1.13	0.5–>16
Penicillin resistant[c] (100)	BAY 12-8039	0.03	0.06	0.04	0.015–0.06
	Clinafloxacin	0.06	0.06	0.05	0.03–0.12
	Trovafloxacin	0.06	0.12	0.09	0.03–0.25
	Sparfloxacin	0.12	0.12	0.14	0.06–0.25
	Levofloxacin	0.5	1	0.72	0.5–1
	Ciprofloxacin	1	1	0.77	0.25–2
	Ofloxacin	1	1	1.02	0.5–2
H. influenzae (330)	BAY 12-8039	0.03	0.06	0.04	0.008–>2
	Clinafloxacin	0.004	0.008	0.006	≤0.002–2
	Trovafloxacin	0.015	0.03	0.02	0.004–>2
	Sparfloxacin	0.015	0.015	0.01	0.004–>2
	Levofloxacin	0.03	0.03	0.03	0.008–>2
	Ciprofloxacin	0.03	0.03	0.03	0.008–>2
	Ofloxacin	0.06	0.06	0.05	0.015–>2
M. catarrhalis (250)	BAY 12-8039	0.06	0.06	0.06	0.03–0.12
	Clinafloxacin	0.008	0.008	0.009	0.008–0.015
	Trovafloxacin	0.008	0.015	0.008	≤0.002–0.015
	Sparfloxacin	0.015	0.015	0.014	0.008–0.03
	Levofloxacin	0.03	0.06	0.04	0.03–0.06
	Ciprofloxacin	0.008	0.015	0.007	≤0.002–0.03
	Ofloxacin	0.06	0.12	0.06	0.008–0.12

[a] Penicillin susceptible is defined by an MIC of ≤0.06 μg/ml.
[b] Penicillin intermediate is defined by an MIC of 0.12 to 1 μg/ml.
[c] Penicillin resistant is defined by an MIC of ≥2 μg/ml.

highest levels of activity against *S. pneumoniae* compared to the other compounds. These values were twofold lower than the MIC_{90}s obtained with sparfloxacin and trovafloxacin and eightfold lower than those obtained with levofloxacin, ofloxacin, or ciprofloxacin. There was no difference in the overall activity of any of the seven agents examined in this study against penicillin-susceptible, -intermediate, or -resistant *S. pneumoniae*. MIC_{50}s and MIC_{90}s were nearly identical for individual antimicrobials, regardless of penicillin susceptibility category. The rank order of activity among this group of fluoroquinolones versus *S. pneumoniae* was as follows: BAY 12-8039 = clinafloxacin > trovafloxacin = sparfloxacin > levofloxacin > ciprofloxacin = ofloxacin.

Two strains of *S. pneumoniae* for which the MICs were conspicuously higher than the range of MICs noted for the general population were detected. The BAY 12-8039, clinafloxacin, trovafloxacin, sparfloxacin, levofloxacin, ciprofloxacin, and ofloxacin MICs for one strain were 1, 0.25, 1, 2, 4, >8, and 8 μg/ml, respectively. For the other strain, the respective MICs were 4, 0.5, 8, 16, 16, >8, and >16 μg/ml. Excluding these two strains, the range of MICs obtained with the seven agents examined in this study versus all isolates of *S. pneumoniae* were as follows: BAY 12-8039, ≤0.004 to 0.06 μg/ml; clinafloxacin, 0.015 to 0.12 μg/ml; trovafloxacin, ≤0.004 to 0.25 μg/ml; sparfloxacin, 0.06–0.25 μg/ml; levofloxacin, 0.25 to 1 μg/ml; ciprofloxacin, 0.25 to 2 μg/ml; and ofloxacin, 0.5 to 2 μg/ml. It is possible that the two strains of *S. pneumoniae* for which the fluoroquinolone MICs were uniformly higher represent resistant organisms. Both of these isolates have proven to be far more refractory to treatment with fluoroquinolones than susceptible strains in a neutropenic murine model of pneumococcal lung infection (data not shown).

The effects of the MIC test format and the incubation atmosphere on BAY 12-8039 MICs versus *S. pneumoniae* were investigated by simultaneously determining the BAY 12-8039 MICs for selected strains by agar dilution and broth microdilution with plates and trays incubated in both CO_2 and ambient air. For the purpose of comparison, ciprofloxacin was also tested in this manner. As can be seen in Table 2, CO_2 incubation led to a marked increase in the MICs of BAY 12-8039 in

TABLE 2. Effect of incubation atmosphere and test format on BAY 12-8039 and ciprofloxacin MICs for *S. pneumoniae.*

Methods compared[a]	No. of strains examined	Antimicrobial	No. of strains yielding the following MIC results:				
			Method A higher		Same	Method B higher	
			Four-fold	Two-fold		Two-fold	Four-fold
AD-CO_2 (A)	9	BAY 12-8039	1	8			
BMD-air (B)		Ciprofloxacin		8	1		
AD-CO_2 (A)	29	BAY 12-8039		14	15		
AD-air (B)		Ciprofloxacin		3	25		
BMD-CO_2 (A)	9	BAY 12-8039		7	2		
BMD-air (B)		Ciprofloxacin		3	5		
AD-CO_2 (A)	9	BAY 12-8039		6	3		
BMD-CO_2 (B)		Ciprofloxacin		3	6		
AD-air (A)	9	BAY 12-8039		8	1		
BMD-air (B)		Ciprofloxacin		5	4		

[a] AD, agar dilution; BMD, broth microdilution.

both test formats. In addition, when the incubation atmosphere was kept constant, MICs determined by agar dilution were consistently lower than MICs determined by broth microdilution. The effects of incubation atmosphere and test format on ciprofloxacin MICs were not as pronounced.

In an attempt to understand the CO_2 effect the pHs of Mueller-Hinton agar supplemented with 5% defibrinated sheep blood (the medium used for agar dilution tests) and MHB plus 5% lysed horse blood (the medium used for broth microdilution MIC determinations) were determined before and after 24-h incubations (with and without antibiotics) in both 5 to 7% CO_2 and ambient air. The initial pH of Mueller-Hinton sheep blood agar was 7.43 to 7.45; after incubation of plates for 24 h in air, the pH range was 7.38 to 7.40; after incubation for the same period in 5 to 7% CO_2, the pH dropped to 6.97 to 6.98. The same pattern was observed with Mueller-Hinton lysed horse blood broth: initial pH, 7.56 to 7.57; pH after 24-h incubation in air, 7.60 to 7.62; pH after 24-h incubation in 5 to 7% CO_2, 6.96 to 6.98.

All seven quinolones displayed high levels of activity against *H. influenzae* and *M. catarrhalis* (Table 1). The MIC_{90}s ranged from 0.008 to 0.06 μg/ml for *H. influenzae* and from 0.008 to 0.12 μg/ml for *M. catarrhalis*. However, as was the case with two isolates of *S. pneumoniae*, one strain of *H. influenzae* seemed to distinguish itself as perhaps being fluoroquinolone resistant; for this strain, the MIC of clinafloxacin was 2 μg/ml and that of the remaining antibiotics was >2 μg/ml.

DISCUSSION

We are unaware of previous published work describing the in vitro activity of BAY 12-8039 versus large numbers of recent clinical isolates of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. A single published study described the activity of BAY 12-8039 versus small numbers of strains (i.e., 30 to 36) of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* taken from a noncontemporary stock culture collection (26). In addition, one abstract at the 1996 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) addressed the in vitro activity of BAY 12-8039 versus all three of these organisms (12). Four others described the activity of BAY 12-8039 versus only *S. pneumoniae* (10, 15, 23, 24). In general, our findings concerning the in vitro activity of BAY 12-8039 versus *H. influenzae* and *M. catarrhalis* are consistent with the observations of previous reports (12, 26). In addition, the absolute and relative in vitro activities of the six other fluoroquinolones examined in this study versus *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* are consistent with the observations of several previously published investigations (3, 4, 9, 21).

Our observations regarding the in vitro activity of BAY 12-8039 versus *S. pneumoniae*, however, differed from those published (26) as well as from those described at the 1996 ICAAC meeting (10, 12, 15, 23, 24). Specifically, the MIC_{50}s and MIC_{90}s we obtained (i.e., 0.03 and 0.06 μg/ml, respectively) were consistently two- to fourfold lower than those previously reported. In an attempt to explain these differences, several study strains were tested simultaneously by agar dilution in CO_2, the method used by previous investigators, and by broth microdilution with trays incubated in ambient air, as was done in the current investigation. Consistently, two- to fourfold-lower MICs were obtained by the latter method. Further experimentation suggested that the noted differences might be due to the effects of CO_2 incubation of agar dilution plates. CO_2 incubation clearly produced a marked pH decrease in test media, perhaps directly diminishing the activity of BAY 12-8039, or perhaps altering the growth characteristics of test strains, in turn leading to a decrease in the expression of BAY 12-8039 activity. In either case, CO_2 incubation of both agar dilution plates and broth microdilution trays resulted in elevated BAY 12-8039 MICs. In addition to this CO_2 effect, it was observed that BAY 12-8039 MICs were consistently higher in the agar dilution format than in the broth microdilution test. Inasmuch as current National Committee for Clinical Laboratory Standards recommendations for quantitative susceptibility testing of *S. pneumoniae* advocate the use of broth microdilution trays incubated in ambient air (18), we assert that the generally lower MICs obtained with BAY 12-8039 versus *S. pneumoniae* in the current study should be considered valid. In view of these observations and assuming acceptable pharmacokinetic and toxicity profiles, clinical trials of BAY 12-8039 for the management of infections caused by the three organisms noted above appear to be warranted.

The results of the current study are also notable for the recognition of two clinical isolates of *S. pneumoniae* and one of *H. influenzae* that appeared to be quinolone resistant. Such strains have been described previously but infrequently (11, 19, 20). Stepwise selection of quinolone resistance in the laboratory has been clearly demonstrated with *S. pneumoniae* (19, 22). This, however, has not been demonstrable with *H. influenzae*. Selection of ciprofloxacin-resistant strains of *S. pneumoniae* has also been observed in patients receiving this agent (19, 20). Quinolone resistance for *S. pneumoniae* has been shown in both laboratory-selected strains and clinical isolates to be the result of primary mutations in the ParC subunit of topoisomerase IV and secondary mutations in the GyrA subunit of DNA gyrase (19). The molecular basis for quinolone resistance in *H. influenzae* has not yet been elucidated. An attempt to define the mutations responsible for the diminished quinolone activity seen in two pneumococcal isolates and in one strain of *H. influenzae* characterized in this study is in progress.

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