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Comparative In Vitro Activities of Sparfloxacin (CI-978; AT-4140) and Other Antimicrobial Agents against Staphylococci, Enterococci, and Respiratory Tract Pathogens

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The in vitro activity of sparfloxacin (CI-978; AT-4140) was compared with those of other antimicrobial agents against isolates of staphylococci, enterococci, and various respiratory tract pathogens. Sparfloxacin was the most active drug tested against staphylococci (MIC for 90% of the strains tested [MIC_{90}], 0.125 μg/ml) and enterococci (MIC_{90}, 1.0 μg/ml). It was also active against *Haemophilus influenzae* (MIC_{90}, ≤0.06 μg/ml), *Moraxella (Branhamella) catarrhalis* (MIC_{90}, 0.125 μg/ml), *Streptococcus pneumoniae* (MIC_{90}, 0.5 μg/ml), and *Streptococcus pyogenes* (MIC_{90}, 1.0 μg/ml).

The fluoroquinolones are a group of synthetic antimicrobial agents with broad-spectrum activity in vitro, favorable pharmacokinetic properties, and established efficacy for the treatment of various infections (6, 19, 20). Staphylococci, including methicillin-susceptible and methicillin-resistant strains, have been found to be susceptible to these agents (1, 8, 20). However, the in vitro activity of currently available quinolones against staphylococci is considerably less than that against members of the family *Enterobacteriaceae* and other gram-negative bacilli. Moreover, the emergence of resistance during therapy for staphylococcal infections with fluoroquinolones has recently been recognized and has been associated with treatment failure (5, 11). Other important pathogens that have been generally less susceptible to these antimicrobial agents have included streptococci and enterococci (1, 10, 20). The marginal activity of currently available fluoroquinolones against *Streptococcus pneumoniae* and *Streptococcus pyogenes* may limit their use in the treatment of respiratory tract infections.

Sparfloxacin (CI-978; AT-4140) is a new fluoroquinolone derivative with potent activity against gram-positive and gram-negative organisms (9, 13). We compared the in vitro activity of sparfloxacin with those of other new fluoroquinolones, β-lactam antibiotics, and standard therapeutic agents against clinical isolates of staphylococci (*Staphylococcus aureus*, *Staphylococcus haemolyticus*, *Staphylococcus saprophyticus*, and other coagulase-negative species), enterococci, and respiratory tract pathogens (*S. pneumoniae*, *S. pyogenes*, *Haemophilus influenzae*, and *Moraxella* [*Branhamella*] *catarrhalis*). A large sample of methicillin-resistant strains were included among the staphylococci, and the *H. influenzae* isolates included a large number of β-lactamase producers.

The bacterial strains used in this study were unique clinical isolates obtained from hospital and private community laboratories across Canada. The organisms had been preserved at −70°C prior to use in the study. Sparfloxacin was provided by Parke-Davis, the Pharmaceutical Division of Warner-Lambert Canada, Inc. All other antimicrobial agents were obtained from their respective manufacturers.

Antimicrobial susceptibility testing was done by a broth microdilution procedure with cation-adjusted Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) and was done in accordance with the guidelines of the National Committee for Clinical Laboratory Standards (14). For susceptibility testing of *S. pneumoniae*, the cation-adjusted Mueller-Hinton broth was supplemented with 3% lysed horse blood. NAD (10 μg/ml) and 3% lysed horse blood were added to the cation-adjusted Mueller-Hinton broth for testing *H. influenzae*. Determination of staphylococcal susceptibility to oxacillin was done with cation-adjusted Mueller-Hinton broth supplemented with 2% NaCl. Each well of a microtiter plate containing 0.1 ml of each antibiotic concentration was inoculated with 0.001 ml of bacterial suspension prepared from an overnight agar culture to achieve a final inoculum of approximately 5×10^5 CFU. The microtiter plates were incubated at 35°C for 18 to 24 h (24 h for *H. influenzae* and staphylococci). The MIC was defined as the lowest concentration of antibiotic that inhibited the development of visible growth in the wells. The following control strains were also tested: *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *H. influenzae* ATCC 35056 (β-lactamase producing).

Table 1 summarizes the comparative in vitro activities of sparfloxacin and other fluoroquinolones against staphylococci and enterococci, expressed as the MICs for 50 and 90% of strains (MIC_{50} and MIC_{90}, respectively) and the range of MICs. Sparfloxacin was the single most active drug tested and was equally active against *S. aureus*, *S. haemolyticus*, *S. saprophyticus*, and other coagulase-negative staphylococci, with 2- to 16-fold-lower MICs. There was no difference in the susceptibilities of methicillin-susceptible and methicillin-resistant strains of *S. aureus* or coagulase-negative staphylococci to sparfloxacin; the MIC_{90} was 0.125 μg/ml. A few of the methicillin-resistant strains of *S. aureus* were also resistant to ciprofloxacin. For two isolates, the ciprofloxacin MICs were 4.0 μg/ml, and for one, the MIC was 8.0 μg/ml. Although susceptibility of these isolates to sparfloxacin was maintained, there was an increase in the MICs for these isolates of all the quinolones tested, including sparfloxacin. Enterococci were generally less susceptible to

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TABLE 1. Comparative in vitro activities of sparfloxacin and other antimicrobial agents against staphylococci and enterococci

Organism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)		
		50%	90%	Range
S. aureus, methicillin susceptible (200)	Sparfloxacin	0.06	0.125	≤0.03–0.25
	Ciprofloxacin	0.5	1.0	≤0.03–1.0
	Lomefloxacin	1.0	1.0	0.25–4.0
	Ofloxacin	0.5	0.5	0.25–1.0
	Temafloxacin	0.25	0.25	0.06–1.0
	Oxacillin	0.5	1.0	≤0.25–2.0
	Vancomycin	2.0	4.0	1.0–8.0
S. aureus, methicillin resistant (160)	Sparfloxacin	0.06	0.125	≤0.03–0.25
	Ciprofloxacin	0.5	2.0	0.125–8.0
	Lomefloxacin	1.0	2.0	0.5–4.0
	Ofloxacin	0.5	1.0	0.25–2.0
	Temafloxacin	0.25	0.5	0.06–1.0
	Oxacillin	>16	>16	8–>16
	Vancomycin	2.0	4.0	1.0–8.0
Coagulase-negative staphylococci, methicillin susceptible (150)	Sparfloxacin	0.06	0.125	≤0.03–0.25
	Ciprofloxacin	0.125	0.25	≤0.03–2.0
	Lomefloxacin	1.0	1.0	0.06–4.0
	Ofloxacin	0.5	0.5	≤0.03–2.0
	Temafloxacin	0.25	0.5	≤0.03–1.0
	Oxacillin	≤0.25	1.0	≤0.25–2.0
	Vancomycin	2.0	2.0	≤0.25–32
Coagulase-negative staphylococci, methicillin resistant (150)	Sparfloxacin	0.06	0.125	≤0.03–1.0
	Ciprofloxacin	0.25	0.25	≤0.03–2.0
	Lomefloxacin	0.5	1.0	0.25–8.0
	Ofloxacin	0.25	0.5	0.125–4.0
	Temafloxacin	0.125	0.25	≤0.03–2.0
	Oxacillin	8.0	>16	4.0–>16
	Vancomycin	2.0	2.0	≤0.25–4.0
S. haemolyticus (100)	Sparfloxacin	0.06	0.125	≤0.03–0.125
	Ciprofloxacin	0.25	0.25	≤0.03–8.0
	Lomefloxacin	0.5	1.0	0.125–1.0
	Ofloxacin	0.25	0.5	0.125–0.5
	Temafloxacin	0.25	0.25	0.06–0.5
	Oxacillin	>16	>16	0.5–>16
	Vancomycin	1.0	2.0	≤0.25–>32
S. saprophyticus (100)	Sparfloxacin	0.125	0.25	≤0.03–0.5
	Ciprofloxacin	0.5	0.5	≤0.03–1.0
	Lomefloxacin	2.0	4.0	0.5–4.0
	Ofloxacin	1.0	1.0	0.25–2.0
	Temafloxacin	0.5	0.5	0.125–1.0
	Oxacillin	1.0	2.0	≤0.25–>16
	Vancomycin	1.0	2.0	0.25–2.0
Enterococcus spp. (100)	Sparfloxacin	0.5	1.0	0.125–1.0
	Ciprofloxacin	1.0	2.0	0.25–2.0
	Lomefloxacin	4.0	8.0	1.0–16
	Ofloxacin	2.0	4.0	0.5–8.0
	Temafloxacin	1.0	2.0	0.25–4.0
	Ampicillin	2.0	2.0	0.5–>8.0
	Vancomycin	4.0	8.0	0.5–16

the fluoroquinolones than were staphylococci, but sparfloxacin was the most active drug (MIC_{90}, 1.0 μg/ml).

The activities of sparfloxacin, other fluoroquinolones, and β-lactam antibiotics against respiratory tract pathogens are shown in Table 2. All the fluoroquinolones were extremely active against both β-lactamase-producing and non-β-lactamase-producing strains of *H. influenzae* (MIC_{90}, ≤0.06 μg/ml). Sparfloxacin was the most active quinolone tested against *S. pneumoniae* (MIC_{90}, 0.5 μg/ml) and *M. catarrhalis* (MIC_{90}, 0.125 μg/ml); sparfloxacin was as active as ciprofloxacin and temafloxacin against *S. pyogenes* (MIC_{90}, 1.0 μg/ml). Of the newer β-lactam antibiotics, BMY 28100 was the most active against *S. pneumoniae* and *S. pyogenes*, ceftibuten was the most active against *H. influenzae*, and loracarbef was the most active against *M. catarrhalis*.

Currently available fluoroquinolones such as norfloxacin, ofloxacin, and ciprofloxacin have become very useful agents for the treatment of various infections due to a variety of microorganisms. These compounds, along with other quinolones, are remarkable for their extremely potent activity

TABLE 2. Comparative in vitro activity of sparfloxacin and other antimicrobial agents against respiratory tract pathogens

Organism (no. of isolates)	Antimicrobial agent	MIC (μg/ml)		
		50%	90%	Range
S. pneumoniae (200)	Sparfloxacin	0.25	0.5	≤0.06–0.5
	Ciprofloxacin	1.0	2.0	0.25–4.0
	Fleroxacin	8.0	8.0	≤0.125–16.0
	Lomefloxacin	4.0	8.0	≤0.125–16.0
	Ofloxacin	2.0	2.0	≤0.125–4.0
	Temafloxacin	0.5	1.0	≤0.125–1.0
	Penicillin	≤0.03	≤0.03	≤0.03–0.125
	Cefuroxime	≤0.25	≤0.25	≤0.25–0.5
	BMY 28100	≤0.25	≤0.25	≤0.25
	Ceftibuten	4.0	4.0	1.0–>32
	Loracarbef	0.5	1.0	≤0.25–2.0
S. pyogenes (200)	Sparfloxacin	0.5	1.0	0.25–2.0
	Ciprofloxacin	0.5	1.0	0.25–2.0
	Fleroxacin	4.0	8.0	1.0–32
	Lomefloxacin	4.0	8.0	1.0–32
	Ofloxacin	1.0	2.0	0.5–4.0
	Temafloxacin	0.5	1.0	0.25–4.0
	Penicillin	≤0.03	≤0.03	≤0.03
	Cefuroxime	≤0.25	≤0.25	≤0.25
	BMY 28100	≤0.06	≤0.06	≤0.06–0.125
	Ceftibuten	≥64	>64	32–>64
	Loracarbef	≤0.25	≤0.25	≤0.25
H. influenzae, β-lactamase negative (100)	Sparfloxacin	≤0.06	≤0.06	≤0.06
	Ciprofloxacin	≤0.06	≤0.06	≤0.06
	Fleroxacin	≤0.06	0.125	≤0.06–0.125
	Lomefloxacin	≤0.06	0.125	≤0.06–0.125
	Ofloxacin	≤0.06	≤0.06	≤0.06–0.125
	Temafloxacin	≤0.06	≤0.06	≤0.06
	Ampicillin	0.5	1.0	0.125–2.0
	Cefuroxime	1.0	4.0	≤0.25–16
	BMY 28100	4.0	16	2.0–64
	Ceftibuten	≤0.06	0.125	≤0.06–0.25
	Loracarbef	4.0	8.0	≤0.25–>32
H. influenzae, β-lactamase positive (100)	Sparfloxacin	≤0.06	≤0.06	≤0.06
	Ciprofloxacin	≤0.06	≤0.06	≤0.06
	Fleroxacin	≤0.06	≤0.06	≤0.06
	Lomefloxacin	≤0.06	0.125	≤0.06–0.25
	Ofloxacin	≤0.06	≤0.06	≤0.06
	Temafloxacin	≤0.06	≤0.06	≤0.06
	Ampicillin	>4	>4	>4
	Cefuroxime	1.0	2.0	≤0.25–8.0
	BMY 28100	16	32	2.0–64
	Ceftibuten	≤0.06	0.125	≤0.06–0.125
	Loracarbef	8.0	32	2–>32
M. catarrhalis, β-lactamase negative (51)	Sparfloxacin	≤0.06	0.125	≤0.06–0.25
	Ciprofloxacin	0.25	0.25	0.125–0.5
	Fleroxacin	1.0	1.0	0.5–2.0
	Lomefloxacin	1.0	1.0	1.0–2.0
	Ofloxacin	0.5	0.5	0.5–1.0
	Temafloxacin	0.25	0.25	0.125–1.0
	Ampicillin	≤0.125	≤0.125	≤0.125–0.5
	Cefuroxime	≤0.25	0.5	≤0.25–1.0
	BMY 28100	0.5	0.5	0.25–1.0
	Ceftibuten	>64	>64	32–>64
	Loracarbef	≤0.25	≤0.25	≤0.25
M. catarrhalis, β-lactamase positive (149)	Sparfloxacin	≤0.06	0.125	≤0.06–0.25
	Ciprofloxacin	0.25	0.25	0.125–0.5
	Fleroxacin	1.0	1.0	0.5–4.0
	Lomefloxacin	1.0	1.0	1.0–2.0
	Ofloxacin	0.5	0.5	0.5–1.0
	Temafloxacin	0.25	0.25	0.125–0.5
	Ampicillin	8.0	16	4.0–>16
	Cefuroxime	1.0	2.0	≤0.25–4.0
	BMY 28100	4.0	8.0	0.25–16
	Ceftibuten	>64	>64	32–>64
	Loracarbef	1.0	4.0	≤0.25–32

against gram-negative organisms, including members of the family *Enterobacteriaceae*, *Campylobacter* spp., *Haemophilus* spp., and *Neisseria* spp. (19, 20). However, gram-positive organisms such as staphylococci, streptococci, and enterococci have been generally less susceptible to available quinolones. For many of these organisms, the MICs of the fluoroquinolones approximate levels of the antimicrobial agents achievable in serum or tissue (20). Thus, treatment with these drugs has been associated with the development of resistance or treatment failure or both in infections due to *S. aureus* (3, 5), methicillin-resistant *S. aureus* (11, 16), *S. saprophyticus* (4), other coagulase-negative staphylococci (17), and *S. pneumoniae* (2). Other studies, reviewed by Wolfson and Hooper (20), of patients treated with quinolones for acute exacerbations of chronic bronchitis due to *S. pneumoniae* found slower clinical responses or failure to eradicate the organism from sputum cultures.

Sparfloxacin is one of several recently described fluoroquinolones (e.g., AM-1091, PD 117,596, and WIN 57273) (7, 15, 18) with more potent in vitro activity against staphylococcal and streptococcal species than those of currently available related compounds. Sparfloxacin also has excellent activity against important gram-negative bacterial pathogens and was found to be bactericidal for clinical isolates at concentrations near the MICs (9). Good in vivo activity in an animal model of systemic infection due to *S. aureus*, *S. pneumoniae*, and *S. pyogenes* was demonstrated by Nakamura and co-workers (13), who also reported that sparfloxacin was well absorbed orally, had a relatively long half-life in plasma, and exhibited good tissue penetration (12). Thus, it appears that sparfloxacin has favorable pharmacokinetic properties and enhanced broad-spectrum activity against a range of organisms that includes both methicillin-susceptible and methicillin-resistant staphylococci, as well as *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, and *M. catarrhalis*. More than other currently available fluoroquinolones, this drug may have a role to play in staphylococcal or respiratory tract infections, although clinical trials will be required to determine its safety and efficacy in treatment of these and other infections.

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