Comparative in vitro activity of trovafloxacin against Gram-negative and Gram-positive pathogens

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*Deniz Gür[1], Sesin Kocagöz[1], Serhat Ünal[1] and Erdal Akalın[1,2]**

[1]Hacettepe University, School of Medicine, Department of Medicine, Section of Infectious Diseases, Ankara, Turkey; [2]Noter Sokak 2/2, Erenköy, Istanbul, Turkey

*Tel: +90 216 302 6105 Fax: +90 216 356 2546

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The frequent use of antibiotics is implicated as the most common cause of the development of resistance [1,2]. Resistance to quinolones was very rare when they were first introduced into clinical practice. However, an increase in resistance to fluoroquinolones has been recently observed, especially in developing countries, where strict rules for antibiotic usage have not yet been established [3,4]. In the present study, the in vitro activity of trovafloxacin (CP-99, 219) was evaluated against 632 clinical isolates and was compared with that of sparfloxacin, ciprofloxacin, and ofloxacin.

All bacteria used in the current study were recovered from clinical sources in the Clinical Microbiology Laboratory, Hacettepe University Hospital, Ankara, Turkey. The exceptions were *Moraxella catarrhalis* strains, which were kindly provided by Dr Bülent Sümerkan, Central Microbiology Laboratory, Erciyes University Hospital, Kayseri, Turkey. *Escherichia coli, Serratia* spp., *Klebsiella* spp., *Enterobacter* spp., *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia* strains were mostly blood isolates, and were identified by the API system (Bio-Merieux, France). *Salmonella* spp. and *Shigella* spp. were isolated from stool cultures, and their identification was confirmed by agglutination with specific antisera (Difco Laboratories, USA). *Proteus* strains were recovered from pus and urine samples. *Streptococcus pneumoniae* and staphylococci were isolated from blood, pus and sterile body sites of hospitalized patients. Methicillin resistance in staphylococci was determined by using oxacillin disks in Mueller–Hinton agar, following the NCCLS guidelines. *Enterococcus* spp. were isolated from various clinical specimens from patients with hospital- or community-acquired infections and were identified according to their biochemical reactions, as previously described [5].

Trovafloxacin was supplied by Pfizer Central Research, USA, ciprofloxacin by Bayer, Turkey, sparfloxacin by Eczacıbaşı-Rhone Poulenc, Turkey, and ofloxacin by Hoechst, Turkey. All agents were supplied as powders, which were diluted according to the manufacturers' instructions. Minimal inhibitory concentrations (MICs) were determined on Mueller–Hinton agar (Merck, Germany) which contained doubling dilutions of antibiotics according to NCCLS criteria [6]. A multipoint inoculator (Denley, UK) was used to inoculate 10^4 CFU bacteria per spot. The results were read after 18 h of incubation. All the antibiotics were tested at the same time.

The MIC_{50} and MIC_{90} values for the isolates are summarized in Table 1. Trovafloxacin and other quinolones had similar in vitro activity against *Escherichia coli*. In addition, the MIC_{90} values of all the quinolones tested against *Enterobacter* spp. and *Klebsiella* spp. exceeded their susceptibility breakpoints. The MIC_{50} values of all agents were also comparable. The activities of the quinolones against *Proteus* spp. were similar (MIC_{90} 1–2 mg/L), with the exception of sparfloxacin (MIC_{90}, 8 mg/L). Trovafloxacin had an in vitro activity similar to that of ofloxacin against *Pseudomonas aeruginosa*, but ciprofloxacin was the most potent antibiotic against this organism. Although *Stenotrophomonas maltophilia* strains are usually resistant to many antimicrobial agents, 50% of these strains were inhibited by all four quinolones tested. Ciprofloxacin was the only agent that inhibited 90% of the strains in *Serratia* isolates. All fluoroquinolones had low MICs (range ≤0.008–2 mg/L) against *Salmonella* spp. and *Shigella* spp. and resistance was not observed for any of the quinolones.

Trovafloxacin was more active in vitro against *Streptococcus pneumoniae* than ciprofloxacin and ofloxacin, and its MIC_{90} value was eight-fold lower than that of ciprofloxacin. The second most active quinolone against pneumococci was sparfloxacin. Of these strains, nine (18%) were intermediately resistant to penicillin and

Table 1 In vitro activity of trovafloxacin and other fluoroquinolones against Gram-negative and Gram-positive pathogens

Organism (number of strains)	Antimicrobial agent	MIC (mg/L)		
		50%	90%	Range
Escherichia coli (49)	Trovafloxacin	0.03	0.125	≤0.008–2
	Sparfloxacin	0.03	0.25	≤0.008–4
	Ciprofloxacin	≤0.008	0.25	≤0.008–2
	Ofloxacin	0.03	0.25	0.03–2
Enterobacter spp. (54)	Trovafloxacin	0.125	>16	0.125 to >16
	Sparfloxacin	0.06	>16	0.03 to >16
	Ciprofloxacin	0.06	4	≤0.008 to >16
	Ofloxacin	0.125	>16	0.03 to >16
Klebsiella spp. (50)	Trovafloxacin	0.25	>16	0.03 to >16
	Sparfloxacin	0.06	>16	0.03 to >16
	Ciprofloxacin	0.06	>16	0.01 to >16
	Ofloxacin	0.125	16	0.03 to >16
Proteus mirabilis (34)	Trovafloxacin	0.50	1.0	≤0.008–1
	Sparfloxacin	0.25	1.0	0.01–4
	Ciprofloxacin	0.03	0.50	≤0.008–1
	Ofloxacin	0.125	2	≤0.008–2
Proteus vulgaris (13)	Trovafloxacin	0.50	2	0.25–4
	Sparfloxacin	0.50	8	0.01–16
	Ciprofloxacin	0.03	2	≤0.008–8
	Ofloxacin	0.125	1	0.08–16
Pseudomonas aeruginosa (50)	Trovafloxacin	2	>16	0.03 to >16
	Sparfloxacin	4	>16	0.01 to >16
	Ciprofloxacin	0.50	>16	≤0.008–8
	Ofloxacin	2	>16	0.06 to >16
Salmonella spp. (41)	Trovafloxacin	0.06	0.25	≤0.008–2
	Sparfloxacin	0.03	0.25	≤0.008–1
	Ciprofloxacin	0.01	0.125	≤0.008–2
	Ofloxacin	0.06	0.125	≤0.008–1
Serratia spp. (61)	Trovafloxacin	2	4	0.125–16
	Sparfloxacin	2	4	0.03 to >16
	Ciprofloxacin	0.25	1	≤0.08–8
	Ofloxacin	0.50	2	0.03–16
Shigella spp. (12)	Trovafloxacin	0.03	0.125	≤0.008–1
	Sparfloxacin	0.01	0.25	≤0.008–2
	Ciprofloxacin	≤0.008	0.06	≤0.008–0.25
	Ofloxacin	0.01	0.25	0.01–0.50
Stenotrophomonas maltophilia (29)	Trovafloxacin	0.50	2	0.125–8
	Sparfloxacin	0.50	4	0.25–8
	Ciprofloxacin	1	4	0.125–8
	Ofloxacin	1	4	0.50–8
Streptococcus pneumoniae (49)	Trovafloxacin	0.06	0.125	0.01–2
	Sparfloxacin	0.125	0.25	0.03–8
	Ciprofloxacin	0.50	1	0.50–4
	Ofloxacin	0.50	2	0.125–8
Enterococcus spp. (40)	Trovafloxacin	0.125	1	0.06–4
	Sparfloxacin	0.50	0.50	0.125–4
	Ciprofloxacin	1	2	0.50–8
	Ofloxacin	1	2	0.50–8

Table 1 *continued*

Organism (number of strains)	Antimicrobial agent	MIC (mg/L) 50%	90%	Range
Moraxella catarrhalis (28)	Trovafloxacin	≤0.008	0.01	≤0.008–0.01
	Sparfloxacin	≤0.008	0.01	≤0.008–0.01
	Ciprofloxacin	0.01	0.01	≤0.008–0.01
	Ofloxacin	0.01	0.03	≤0.008–0.03
Staphylococcus aureus, methicillin resistant (29)	Trovafloxacin	1	8	0.03–16
	Sparfloxacin	8	>16	0.06 to >16
	Ciprofloxacin	8	>16	0.03 to >16
	Ofloxacin	8	>16	0.03 to >16
Staphylococcus aureus, methicillin sensitive (31)	Trovafloxacin	0.01	0.25	≤0.008–2
	Sparfloxacin	0.06	0.50	0.03–8
	Ciprofloxacin	0.25	0.50	0.125–8
	Ofloxacin	0.25	1	0.125–8
Coagulase-negative *Staphylococcus*, methicillin resistant (17)	Trovafloxacin	0.50	16	≤0.008–16
	Sparfloxacin	4	>16	0.03 to >16
	Ciprofloxacin	2	>16	0.125 to >16
	Ofloxacin	4	>16	0.125 to >16
Coagulase-negative *Staphylococcus*, methicillin sensitive (45)	Trovafloxacin	0.03	0.25	≤0.008–2
	Sparfloxacin	0.125	1	0.01–16
	Ciprofloxacin	0.125	0.50	0.03–16
	Ofloxacin	0.25	2	0.06–16

two had high level resistance to penicillin. All quinolones showed equal in vitro activity against *Moraxella catarrhalis*, and MIC_{90} values were lower than their susceptibility breakpoints. Against enterococci, sparfloxacin was the agent with the lowest MIC_{90} value (0.5 mg/L), followed by trovafloxacin (1 mg/L). Among staphylococci, strains resistant to methicillin were also resistant to the quinolones tested. Trovafloxacin was the only agent that inhibited 50% of the methicillin-resistant staphylococci (1 mg/L). Furthermore, in methicillin-susceptible strains, trovafloxacin (MIC_{90} 0.25 mg/L) demonstrated two-fold greater activity than ciprofloxacin (MIC_{90} 0.5 mg/L).

The current study indicates that a wide range of Gram-negative and Gram-positive bacteria isolated from clinically important infections are susceptible to trovafloxacin. Furthermore, trovafloxacin was active against 50% of the methicillin-resistant staphylococcal strains.

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