

In Vitro Activity of Garenoxacin Tested Against Ciprofloxacin-Susceptible and -Resistant Enterobacteriaceae and *Acinetobacter* spp. Strains Collected Worldwide by the SENTRY Antimicrobial Surveillance Program (2004 - 2005)

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Abstract

Objective: To evaluate the contemporary activity of garenoxacin (GRN) against ciprofloxacin (CIPRO)-susceptible (S) and CIPRO-resistant (R) Enterobacteriaceae (ENT) and *Acinetobacter* spp. (ASP). Unlike recently marketed fluoroquinolones (FQ), GRN lacks a fluorine at the C-6 position.

Methods: A total of 9,017 isolates (8,247 ENT and 770 ASP) were consecutively collected from > 70 medical centers from bloodstream, respiratory, urinary and skin and soft tissue infections and tested by reference broth microdilution methods according to CLSI/NCCLS methods and interpretative criteria. A GRN-S breakpoint of ≤ 1 mg/L was applied for comparison purposes only.

Results: The results of the major organism groups tested:

Organism (no. CIPRO-S/R)	GRN (MIC ₅₀ in mg/L/% S)		
	CIPRO-S	CIPRO-R	All strains
<i>Citrobacter</i> spp. (173/20)	0.06/85.5	>4/0.0	0.12/76.7
<i>E. cloacae</i> (675/103)	0.12/93.3	>4/1.9	0.12/81.2
<i>E. coli</i> (3,040/679)	<=0.03/98.9	>4/0.4	<=0.03/80.9
<i>K. pneumoniae</i> (1,308/230)	0.12/95.9	>4/3.5	0.12/82.1
<i>P. mirabilis</i> (340/94)	0.25/92.6	>4/1.1	0.25/72.8
<i>Salmonella</i> spp. (134/0)	0.06/99.3	-	0.06/99.3
<i>Serratia</i> spp. (459/31)	1/59.0	>4/0.0	1/55.3
All ENT (6,985/1,262)	0.06/94.0	>4/1.2	0.12/79.8
ASP (503/267)	<=0.03/97.0	>4/3.6	4/36.0

GRN showed good activity against this large collection of ENT (MIC₅₀, 0.12 mg/L) and 79.8% of isolates were inhibited at ≤ 1 mg/L. The activity (MIC₅₀/%S) of other oral antimicrobials tested against ENT was: amoxicillin/clavulanate 8/62.2%, cefuroxime 4/58.2%, gatifloxacin ≤ 0.5 /85.9%, levofloxacin ≤ 0.5 /85.9%, moxifloxacin 0.06/84.7%, trimethoprim/sulfamethoxazole ≤ 0.5 /74.4%. The in vitro activity of GRN was most similar to that of CIPRO. Among CIP-S ENT (6,985 isolates), 94.0% (59.0-99.3%) were S to GRN, while among CIPRO-S ASP, 97.0% were S to GRN. 97.2% of CIP-R ENT isolates were also R to GRN.

Conclusions: GRN in vitro activity was similar to that of the several commonly used FQs and superior to other tested orally administered agents when tested against contemporary (2004 - 2005) ENT and ASP isolates.

Introduction

Garenoxacin, a novel des-F(6)-quinolone, has a structure that lacks the C6-position fluorine, but has a unique difluoromethoxy substitution at position C8. These alterations favorably influence potency against both DNA gyrases and topoisomerase IV at achievable human serum concentrations following 400 mg doses by oral or intravenous routes.

Garenoxacin has been described as highly active against important Gram-positive and -negative pathogens and atypical respiratory tract pathogens (*Mycoplasmas*, *C. pneumoniae*, and *Legionella* spp.). These features are complemented by the high probability of favorable PD target attainment (AUC/MIC) that leads to successful bacterial eradications and minimization of mutational events among indicated species, e.g. low MPC values. The combination of spectrum coverage and potency favors garenoxacin use for 1) community-acquired respiratory tract infections (CA-RTI; hospitalized or ambulatory patients); 2) skin and soft tissue infections (complicated with mixed flora or uncomplicated); and 3) selected community-acquired intra-abdominal infection indications.

The in vitro testing results for garenoxacin from the 2004 - 2005 period of the SENTRY Antimicrobial Surveillance Program were summarized to assess the spectrum and potency versus a very large collection of Enterobacteriaceae. A total of 9,017 isolates (8,247 Enterobacteriaceae and 770 *Acinetobacter* spp.) were analyzed from results generated by the reference methods.

Materials and Methods

Susceptibility testing. All MIC values presented were produced by broth microdilution methods (CLSI, M7-A7) in panels produced by TREK Diagnostics (Cleveland, Ohio, USA). Concurrent quality assurance was maintained via use of CLSI-recommended strains: *E. coli* ATCC 25922 and 35218; *P. aeruginosa* ATCC 27583; *E. faecalis* ATCC 29212; *S. aureus* ATCC 25923 and 29213. All quality control results were within published MIC ranges (CLSI, M100-S16). Approximately 35 - 40 different antimicrobial agents were processed each year with selected agents compared to garenoxacin in this presentation. A breakpoint for garenoxacin at ≤ 1 mg/L was tentatively used for comparison purposes only.

Bacterial strains. The organisms were consecutively collected isolates processed in a central laboratory system (JMI Laboratories, North Liberty, Iowa, USA) using common reference test reagents. Isolates were derived from a wide variety of clinical sources (Program Objectives) such as: bloodstream, community-acquired or nosocomial respiratory tract sites, skin and soft tissue infections, urinary tract infections and selected patient populations. In this investigation, the isolates were obtained from a wide variety of infections at medical centers in North America (≥ 25 sites in the USA and Canada), Latin America (10 sites) and Europe (≥ 25 sites). The distribution of tested species was: Enterobacteriaceae (8,247 isolates) and *Acinetobacter* spp. (770 isolates), selected from the SENTRY Antimicrobial Surveillance Program for the years 2004 and 2005.

Results

Table 1 lists the most commonly isolated Enterobacteriaceae, worldwide, in the SENTRY Program. *E. coli* was clearly the most prevalent pathogen (41.2%) followed by *Klebsiella pneumoniae* (17.1%) and *Enterobacter cloacae* (8.6%). These three pathogens represented almost 70% of Enterobacteriaceae collected in the 2004 - 2005 period.

Among the 3,719 *E. coli* tested only 72.4% were susceptible to cefuroxime axetil (oral), 79.2% to amoxicillin/clavulanate and 67.0% to trimethoprim/sulfamethoxazole. ESBL phenotypes were observed in 7.6% of strains and all tested fluoroquinolones had a similar coverage (% susceptible) for *E. coli* (80.9 - 82.0%).

Garenoxacin inhibition of *K. pneumoniae* and *Enterobacter cloacae* at ≤ 1 mg/L (82.1% for both pathogens) was slightly less than that of ciprofloxacin (85.0 and 86.8%, respectively), gatifloxacin (87.9 and 89.1%, respectively) and levofloxacin (86.7 and 88.8%, respectively) at their respective susceptible breakpoints. ESBL phenotypes were more prevalent among *K. pneumoniae* (26.7%) compared to other Enterobacteriaceae.

Ciprofloxacin, gatifloxacin, and levofloxacin showed similar spectrums against *Citrobacter* spp. (89.6 - 90.2%) and *Serratia* spp. (93.7-94.7%), while garenoxacin activities against these pathogens were more limited (76.7 and 55.3% susceptibility, respectively).

Salmonella spp. (134 isolates) was highly susceptible (100.0%) to all tested quinolones (Table 1). Resistance rates for all classes generally were at $\leq 3\%$, but only 58.2% were considered susceptible to cefuroxime axetil.

Table 1. Frequency of occurrence of Enterobacteriaceae species/genera.

Rank	Species/genus group	No. tested (%)
1	<i>E. coli</i>	3,719 (41.2)
2	<i>K. pneumoniae</i>	1,538 (17.1)
3	<i>E. cloacae</i>	778 (8.6)
4	<i>Serratia</i> spp.	490 (5.4)
5	<i>Proteus mirabilis</i>	434 (4.8)
6	<i>K. oxytoca</i>	297 (3.3)
7	<i>E. aerogenes</i>	209 (2.3)
8	Indole-positive <i>Proteae</i>	194 (2.2)
9	<i>Citrobacter</i> spp.	193 (2.1)
10	<i>Salmonella</i> spp.	134 (1.5)

Table 2. In vitro activity of garenoxacin and comparator agents tested against Enterobacteriaceae and *Acinetobacter* spp. (SENTRY Program, 2004 - 2005).

Organism (no. tested)/ Antimicrobial agent	MIC (mg/L)		% by category: ^a		Organism (no. tested)/ Antimicrobial agent	MIC (mg/L)		% by category: ^a		Organism (no. tested)/ Antimicrobial agent	MIC (mg/L)		% by category: ^a		
	50%	90%	Susceptible	Resistant		50%	90%	Susceptible	Resistant		50%	90%	Susceptible	Resistant	
<i>Citrobacter</i> spp. (193)															
Garenoxacin	0.12	4	76.7 ^b	13.5	Garenoxacin	0.12	>4	82.1 ^b	16.7	<i>Serratia</i> spp. (490)	1	4	55.3 ^b	18.8	
Ciprofloxacin	≤ 0.25	1	89.6	9.3	Ciprofloxacin	≤ 0.25	>4	85.0	13.2	Ciprofloxacin	≤ 0.25	1	93.7	5.3	
Gatifloxacin	≤ 0.03	2	90.2	6.7	Gatifloxacin	0.06	>4	87.9	10.2	Gatifloxacin	0.25	2	94.3	3.9	
Levofloxacin	≤ 0.03	2	90.2	7.8	Levofloxacin	0.06	>4	86.7	11.2	Levofloxacin	0.12	1	94.7	3.5	
Moxifloxacin	0.12	4	-	-	Moxifloxacin	0.12	>4	-	-	Moxifloxacin	0.5	2	-	-	
Amoxicillin/Clavulanate	>16	>16	37.5	54.2	Amoxicillin/Clavulanate	4	16	74.8	9.4	Amoxicillin/Clavulanate	>16	>16	2.7	95.3	
Cefuroxime	4	>16	57.0	25.9	Cefuroxime	4	>16	62.9	24.4	Cefuroxime	>16	>16	0.4	94.5	
Trim/sulfa ^d	≤ 0.5	>2	83.4	16.6	Trim/sulfa ^d	≤ 0.5	>2	75.3	24.7	Trim/sulfa ^d	≤ 0.5	2	91.4	8.6	
<i>E. cloacae</i> (778)															
Garenoxacin	0.12	>4	81.2 ^b	16.6	Garenoxacin	0.25	>4	72.8 ^b	24.3	Enterobacteriaceae (8,247)	0.12	>4	79.8 ^b	17.3	
Ciprofloxacin	≤ 0.25	>2	86.8	10.8	Ciprofloxacin	≤ 0.25	>2	78.3	16.4	Ciprofloxacin	≤ 0.25	>2	84.7	14.2	
Gatifloxacin	≤ 0.03	2	89.1	8.4	Gatifloxacin	0.12	>4	79.7	14.5	Gatifloxacin	≤ 0.03	>4	85.9	10.8	
Levofloxacin	≤ 0.03	4	88.8	9.0	Levofloxacin	0.06	>4	85.3	11.1	Levofloxacin	≤ 0.03	>4	85.9	11.9	
Moxifloxacin	0.06	>4	-	-	Moxifloxacin	0.25	>4	-	-	Moxifloxacin	0.06	>4	-	-	
Amoxicillin/Clavulanate	>16	>16	3.7	94.2	Amoxicillin/Clavulanate	≤ 1	8	92.4	2.8	Amoxicillin/Clavulanate	8	>16	62.2	26.5	
Cefuroxime	16	>16	14.0	43.6	Cefuroxime	1	4	90.6	6.7	Cefuroxime	4	>16	58.2	23.0	
Trim/sulfa ^d	≤ 0.5	>2	82.6	17.4	Trim/sulfa ^d	≤ 0.5	>2	66.8	33.2	Trim/sulfa ^d	≤ 0.5	>2	74.4	25.6	
<i>E. coli</i> (3,719)															
Garenoxacin	≤ 0.03	>4	80.9 ^b	18.6	Garenoxacin	0.06	0.25	100.0 ^b	0.0	<i>Acinetobacter</i> spp. (770)	4	>4	36.0 ^b	61.6	
Ciprofloxacin	≤ 0.25	>2	81.7	18.2	Ciprofloxacin	≤ 0.25	≤ 0.25	100.0	0.0	Garenoxacin	4	>2	34.7	64.5	
Gatifloxacin	≤ 0.03	4	82.0	13.6	Gatifloxacin	≤ 0.03	0.12	100.0	0.0	Ciprofloxacin	>4	>2	39.1	42.9	
Levofloxacin	≤ 0.03	>4	81.9	15.9	Levofloxacin	0.06	0.25	100.0	0.0	Gatifloxacin	>4	>4	37.1	53.0	
Moxifloxacin	≤ 0.03	>4	-	-	Moxifloxacin	0.12	0.5	-	-	Levofloxacin	4	>4	-	-	
Amoxicillin/Clavulanate	8	16	79.2	6.0	Amoxicillin/Clavulanate	≤ 1	8	91.0	0.7	Moxifloxacin	4	>4	34.1	34.1	
Cefuroxime	4	16	72.4	7.7	Cefuroxime	4	8	58.2	2.2	Amoxicillin/sulbactam	8	>32	51.8	6.6	
Trim/sulfa ^d	≤ 0.5	>2	67.0	33.0	Trim/sulfa ^d	≤ 0.5	≤ 0.5	97.0	3.0	Cefuroxime	>16	>16	6.6	88.2	
					Trim/sulfa ^d	≤ 0.5	≤ 0.5	97.0	3.0	Trim/sulfa ^d	>2	>2	37.5	62.5	

a. Susceptibility criteria of CLSI (2006), where available.
b. Susceptibility defined as ≤ 1 mg/L for garenoxacin for comparison purposes only.
c. - = no susceptibility criteria available (CLSI, 2006).
d. Trim/sulfa = Trimethoprim/sulfamethoxazole.

Table 3. Activity of garenoxacin and comparator agents against ciprofloxacin-susceptible and -resistant organisms.

Organism (no tested: ciprofloxacin susceptible/resistant)	% Susceptible		% Resistant	
	Ciprofloxacin- susceptible/resistant	Ciprofloxacin- susceptible/resistant	Ciprofloxacin- susceptible/resistant	Ciprofloxacin- susceptible/resistant
<i>Citrobacter</i> spp. (173/20)				
Garenoxacin	85.5/0.0	3.5/100.0		
Gatifloxacin	100.0/5.0	0.0/65.0		
Levofloxacin	100.0/5.0	0.0/75.0		
Amoxicillin/clavulanate	40.1/15.0	51.2/80.0		
Cefuroxime	61.8/15.0	21.4/65.0		
Trimethoprim/sulfamethoxazole	89.6/30.0	10.4/70.0		
<i>E. cloacae</i> (675/103)				
Garenoxacin	93.3/1.9	4.7/94.2		
Gatifloxacin	99.6/20.4	0.1/62.1		
Levofloxacin	99.6/18.4	0.1/67.0		
Amoxicillin/clavulanate	4.1/1.0	93.8/97.1		
Cefuroxime	16.1/0.0	35.9/94.2		
Trimethoprim/sulfamethoxazole	89.2/39.8	10.8/60.2		
<i>E. coli</i> (3,040/679)				
Garenoxacin	98.9/0.4	0.6/99.1		
Gatifloxacin	>99.9/1.5	<0.1/74.2		
Levofloxacin	100.0/0.9	0.0/87.3		
Amoxicillin/clavulanate	85.6/50.5	3.4/17.5		
Cefuroxime	81.3/32.7	2.6/30.6		
Trimethoprim/sulfamethoxazole	75.4/29.2	24.6/70.8		
<i>K. pneumoniae</i> (1,308/230)				
Garenoxacin	95.9/3.5	1.6/93.0		
Gatifloxacin	100.0/19.1	0.0/68.3		
Levofloxacin	99.9/11.7	0.0/74.8		
Amoxicillin/clavulanate	84.3/20.9	4.4/37.4		
Cefuroxime	73.3/3.9	14.8/79.1		
Trimethoprim/sulfamethoxazole	85.3/18.3	14.7/81.7		
<i>P. mirabilis</i> (340/94)				
Garenoxacin	92.6/1.1	6.8/98.9		
Gatifloxacin	98.8/10.6	0.0/67.0		
Levofloxacin	100.0/31.9	0.0/51.1		
Amoxicillin/clavulanate	94.7/94.0	1.5/7.4		
Cefuroxime	95.9/71.3	2.9/20.2		
Trimethoprim/sulfamethoxazole	79.7/20.2	20.3/79.8		
<i>Serratia</i> spp. (459/31)				
Garenoxacin	59.0/0.0	13.3/100.0		
Gatifloxacin	99.3/19.4	0.0/61.3		
Levofloxacin	100.0/16.1	0.0/54.8		
Amoxicillin/clavulanate	2.6/3.2	95.2/96.8		
Cefuroxime	0.4/19.4	94.1/38.7		
Trimethoprim/sulfamethoxazole	95.6/29.0	4.4/71.0		
All Enterobacteriaceae (6,985/1,262)				
Garenoxacin	94.0/1.2	2.8/97.2		
Gatifloxacin	99.8/8.8	0.0/70.5		
Levofloxacin	99.9/8.3	0.0/77.8		
Amoxicillin/clavulanate	66.5/38.4	25.0/34.7		
Cefuroxime	64.2/24.8	18.0/50.5		
Trimethoprim/sulfamethoxazole	82.6/28.8	17.4/71.2		
<i>Acinetobacter</i> spp. (267/503)				
Garenoxacin	97.0/3.6	1.9/93.2		
Gatifloxacin	98.5/7.6	1.5/64.8		
Levofloxacin	98.5/4.6	1.9/80.3		
Ampicillin/sulbactam	88.0/32.8	6.0/49.1		
Cefuroxime	7.9/0.6	67.8/99.0		
Trimethoprim/sulfamethoxazole	86.5/11.5	13.5/88.5		

Against Enterobacteriaceae in general, the spectrum (% susceptible) of garenoxacin (79.8%) was slightly lower than those of ciprofloxacin (84.7%), gatifloxacin