

In Vitro Activity of Nemonoxacin, a Novel Nonfluorinated Quinolone, against 2,440 Clinical Isolates[∇]

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The in vitro activity of nemonoxacin (TG-873870), a novel nonfluorinated quinolone, was tested against 2,440 clinical isolates. Nemonoxacin was at least fourfold more active than levofloxacin and moxifloxacin against most gram-positive cocci tested (shown by the following MIC₉₀/range [μg/ml] values; community-associated methicillin [meticillin]-resistant *Staphylococcus aureus*, 0.5/0.015 to 2; *Staphylococcus epidermidis*, 0.5/0.015 to 4 for methicillin-susceptible staphylococci and 2/0.12 to 2 for methicillin-resistant staphylococci; *Streptococcus pneumoniae*, 0.015/≤0.008 to 0.25; *Enterococcus faecalis*, 1/0.03 to 128). Nemonoxacin activity against gram-negative bacilli was similar to levofloxacin and moxifloxacin (MIC₉₀/range [μg/ml]; *Escherichia coli*, 32/≤0.015 to ≥512; *Klebsiella pneumoniae*, 2/≤0.015 to 128; *K. oxytoca*, 0.5/0.06 to 1; *Proteus mirabilis*, 16/0.25 to ≥512; *Pseudomonas aeruginosa*, 32/≤0.015 to ≥512; *Acinetobacter baumannii*, 1/0.12 to 16).

Nemonoxacin (TG-873870) (TaiGen Biotechnology Co. Ltd.) is a novel C-8-methoxy nonfluorinated quinolone that is currently being investigated for clinical use (Fig. 1). On the basis of other fluoroquinolones with similar chemical structures, nemonoxacin is expected to have a broad spectrum of activity and reduced toxicity. C-8-methoxy substituents have been associated with an improved spectrum of activity, including increased activity against gram-positive cocci, and reduced mutant selection (1, 13). The removal of the fluorine residue may reduce the incidence of toxic side effects (2).

The activity of nemonoxacin against *Mycobacterium tuberculosis* and *Nocardia* spp. has been described previously (9, 15). Current studies with nemonoxacin indicate that it is active against a variety of gram-negative and gram-positive organisms, including antibiotic-resistant organisms like methicillin (meticillin)-resistant *Staphylococcus aureus* (MRSA) (8, 12, 16). Good safety and efficacy data have been reported for animal studies (6–8). Nemonoxacin was noted to have a safety profile similar to that of levofloxacin in the treatment of community-acquired pneumonia (16).

The purpose of this study was to assess the activity of nemonoxacin and other fluoroquinolones against gram-positive and gram-negative organisms obtained from Canadian hospitals as part of the CANWARD 2007 study. The most prevalent gram-positive and gram-negative pathogens collected as part of the CANWARD study (www.can-r.ca) were included in this analysis.

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Clinical isolates were collected as part of CANWARD, an ongoing national surveillance system designed to assess pathogen prevalence and antibiotic resistance from respiratory, skin and soft tissue, urinary, and bacteremic infections in Canadian hospitals (18). Twelve sentinel hospitals from across Canada submitted clinical isolates from blood, respiratory, urine, and wound/intravenous site specimens from patients affiliated with hospital clinics, emergency rooms, medical/surgical wards, and intensive care units. All organisms were deemed clinically significant and identified at the originating center using local site criteria.

The organisms evaluated in this study included 374 methicillin-susceptible *S. aureus* (MSSA) isolates, 127 MRSA (25 community-associated MRSA [CA-MRSA] isolates and 99 hospital-associated MRSA [HA-MRSA] isolates), 43 methicillin-susceptible *Staphylococcus epidermidis* (MSSE) isolates, 9 methicillin-resistant *S. epidermidis* (MRSE) isolates, 655 *Streptococcus pneumoniae* isolates (including 32 penicillin-resistant isolates), 81 *Enterococcus faecalis* isolates, 38 *Enterococcus faecium* isolates, 599 *Escherichia coli* isolates, 199 *Klebsiella pneumoniae* isolates, 32 *Klebsiella oxytoca* isolates, 72 *Enterobacter cloacae* isolates, 33 *Proteus mirabilis* isolates, 137 *Pseudomonas aeruginosa* isolates, 26 *Stenotrophomonas maltophilia* isolates, and 15 *Acinetobacter baumannii* isolates.

In vitro susceptibilities were determined by the broth microdi-

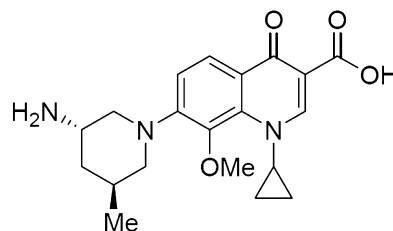


FIG. 1. Nemonoxacin chemical structure. Me, methyl group.

Species (n)	Agent	<i>E. faecalis</i> (81)				<i>E. faecium</i> (38)									
		Count	(%)	Count	(%)	Count	(%)	Count	(%)						
<i>E. faecalis</i> (81)	NMX	2	(2.5)	13	(18.5)	31	(56.8)	9	(67.9)	16	(90.1)	6	(97.5)	1	(98.8)
	CIP					2	(2.5)	2	(2.5)	27	(43.2)	17	(64.2)	1	(66.7)
	LVX			1 ^c	(1.2)	3	(4.9)	32	(44.4)	27	(55.8)	26	(67.9)	2	(66.7)
	MXF									2	(67.9)			4	(72.8)
<i>E. faecium</i> (38)	NMX			3	(7.9)	3	(15.8)	5	(28.9)	6	(15.8)	1	(31.6)	4	(42.1)
	CIP									4	(10.5)	3	(23.7)	1	(26.3)
	LVX									4	(10.5)	5	(23.7)	2	(28.9)
	MXF							5	(13.2)	3	(26.3)	2	(28.9)	1	(28.9)

^a FQ, fluoroquinolone; NMX, nemonoxacin; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin.
^b The numbers of isolates and cumulative percentages for MIC₉₀ values are shown in boldface type.
^c Lowest concentration tested. The actual MICs of some isolates may be lower than indicated.
^d Highest MICs of some isolates may be higher than indicated.

lution method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (3). The fluoroquinolones tested in this study included ciprofloxacin, levofloxacin, moxifloxacin, and nemonoxacin. Custom-designed 96-well microdilution panels containing doubling dilutions of the antimicrobial agents in cation-adjusted Mueller-Hinton broth with 5% lysed horse blood were produced to determine the MICs. Quality control of the broth microdilution panels was conducted using appropriate CLSI organisms and MIC ranges (3). Quality control for nemonoxacin was performed using the following ATCC quality control organisms with moxifloxacin ranges: *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853. MICs were interpreted on the basis of CLSI breakpoints (4).

MRSA were assigned to the Canadian epidemic strain types (CMRSA-1 to CMRSA-10) (14) by pulsed-field gel electrophoresis (PFGE) or staphylococcal protein A (*spa*) typing (5, 10) as previously described (11). CA-MRSA and HA-MRSA were differentiated genotypically (by PFGE pattern), as epidemiologic data were unavailable (11). CMRSA-7 (USA400) and CMRSA-10 (USA300) isolates were identified as CA-MRSA, while organisms with all other CMRSA patterns were considered HA-MRSA. Isolates that were not assigned to one of the epidemic strains by PFGE or *spa* typing were labeled “unique” and were not considered HA-MRSA or CA-MRSA (11).

In 2007, 7,881 clinical isolates were collected as part of CANWARD (18). The in vitro activity of nemonoxacin was tested against 2,440 gram-positive cocci and gram-negative bacilli.

Table 1 presents the MIC distributions and MIC₉₀s for nemonoxacin and other fluoroquinolones against gram-positive cocci. Nemonoxacin displayed greater activity than the other fluoroquinolones tested against the MSSA (MIC₉₀, 0.12 µg/ml). In addition, nemonoxacin displayed slightly greater activity than the other fluoroquinolones tested against the MRSA (nemonoxacin, 4 µg/ml; ciprofloxacin, ≥16 µg/ml; levofloxacin, ≥32 µg/ml; moxifloxacin, 8 µg/ml [MIC₅₀s shown]). The activity of all of the fluoroquinolones was reduced against MRSA, but nemonoxacin was the least affected (Table 1). The higher nemonoxacin MICs of ≥4 µg/ml were noted only among the HA-MRSA that displayed high levels of resistance to levofloxacin and moxifloxacin. By PFGE, the majority of these isolates were genetically unrelated to other strains in the study (40%) or were in small clusters of two or three isolates (28%) (11). Interestingly, nemonoxacin remained highly active against CA-MRSA (MIC₅₀, 0.25 µg/ml; MIC₉₀, 0.5 µg/ml). The activity of nemonoxacin was significantly greater against *S. aureus* with levofloxacin MICs of <2 µg/ml (MIC₉₀, 0.06 µg/ml) than isolates with levofloxacin MICs of ≥2 µg/ml (MIC₉₀, 16 µg/ml). Nemonoxacin was at least eightfold more active than the other fluoroquinolones against *S. epidermidis* (MSSE and MRSE). The activity of nemonoxacin against *S. pneumoniae* (MIC₉₀, 0.015 µg/ml), including penicillin-resistant strains (MIC₉₀, 0.03 µg/ml), was the greatest of the fluoroquinolones tested. Similarly, nemonoxacin was the most active fluoroquinolone against *E. faecalis*. Nemonoxacin was more active against *E. faecalis* (MIC₉₀, 1 µg/ml) than *E. faecium* (MIC₉₀, 128 µg/ml).

The activity of nemonoxacin and other fluoroquinolones against gram-negative bacilli is displayed in Table 2 as MIC

TABLE 2. In vitro activity of nemoxacin and other antimicrobials against gram-negative bacilli

Organism (n)	FQ ^a	No. of isolates (% [cumulative]) with the following MIC ($\mu\text{g/ml}$) ^b :															
		≤ 0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256	≥ 512
<i>E. coli</i> (599)	NMX	1 ^c (0.2)	8 (1.5)	127 (22.7)	211 (57.9)	65 (68.8)	22 (72.5)	14 (74.8)	4 (75.5)	2 (75.8)	27 (80.1)	20 (79.1)	84 (93.2)	30 (98.2)	7 (99.3)	2 (99.7)	2 ^d (100)
	CIP			404 ^c (67.4)	10 (69.1)	22 (72.8)	8 (74.1)	7 (75.3)	1 (75.5)	1 (75.6)	1 (75.6)	119^d (100)					
	LVX			398 ^c (66.4)	8 (67.8)	13 (70)	22 (73.6)	9 (75.1)	3 (75.5)	3 (75.6)	17 (78.5)	84 (92.5)					
	MXF			361 ^c (60.3)	41 (67.1)	10 (68.8)	28 (73.5)	10 (75.1)	2 (75.5)	11 (77.3)	18 (80.3)	118^d (100)					
<i>K. pneumoniae</i> (199)	NMX	1 ^c (0.5)	1 (1)	1 (1.5)	51 (27.1)	82 (68.3)	19 (77.9)	18 (86.9)	10 (92)	4 (94)	2 (95)	1 (95.5)	5 (98)	1 (98.5)	3 (100)		
	CIP			147 ^c (73.9)	12 (79.9)	11 (85.4)	12 (91.5)	1 (92)	2 (93)	1 (93.5)	2 (94.5)	11^d (100)					
	LVX			139 ^c (69.8)	15 (77.4)	2 (78.4)	18 (87.4)	10 (92.5)	1 (93)	6 (96)		5 (98.5)	3^d (100)				
	MXF			48 ^c (24.1)	96 (72.4)	11 (77.9)	12 (83.9)	15 (91.5)	3 (93)	3 (94.5)	3 (96)	8 ^d (100)					
<i>K. oxytoca</i> (32)	NMX			2 (6.3)	7 (28.1)	17 (81.3)	5 (96.9)	1 (100)									
	CIP			30^f (93.8)	1 (66.9)	1 (100)											
	LVX			30^f (93.8)	2 (100)												
	MXF			15 ^c (46.9)	15 (93.8)	2 (100)											
<i>E. cloacae</i> (72)	NMX			6 (8.3)	31 (51.4)	23 (83.3)	5 (90.3)	1 (91.7)	1 (91.7)	1 (93.1)	2 (95.8)	2 (98.6)	1 (100)				
	CIP			64 ^c (88.9)	1 (90.3)	2 (90.3)	1 (91.7)	1 (91.7)	1 (93.1)	4 (97.2)	1 (98.6)	1 (100)					
	LVX			63 ^c (87.5)	2 (90.3)	2 (90.3)	1 (91.7)	1 (91.7)	1 (93.1)	3 (97.2)	1 (98.6)	1 (100)					
	MXF			49 ^c (68.1)	14 (87.5)	2 (90.3)	1 (91.7)	1 (91.7)	1 (94.4)	3 (98.6)	1 ^d (100)						
<i>P. mirabilis</i> (33)	NMX			21 ^c (63.6)	3 (72.7)	8 (24.2)	10 (54.5)	7 (75.8)	1 (78.8)	1 (81.8)	1 (81.8)	3 (90.9)	1 (97)	1 (97)	1 (97)	1 ^d (100)	
	CIP			11 ^c (33.3)	10 (63.6)	4 (75.8)	1 (78.8)	1 (78.8)	2 (84.8)	3 (93.9)	1 (97)	1 ^d (100)					
	LVX			1 (3)	9 (30.3)	11 (63.6)	5 (78.8)	5 (78.8)	1 (81.8)	1 (81.8)	1 (84.8)	5^d (100)					
	MXF																
<i>P. aeruginosa</i> (137)	NMX	1 ^c (0.7)		2 (2.2)	3 (4.4)	14 (14.6)	50 (51.1)	21 (66.4)	16 (78.1)	1 (78.8)	10 (86.1)	7 (91.2)	6 (95.6)	3 (97.8)	2 (99.3)	1 ^d (100)	
	CIP			28 (27.7)	35 (53.3)	16 (65)	13 (74.5)	7 (79.6)	8 (85.4)	7 (90.5)	13 ^d (100)						
	LVX			4 (5.1)	7 (10.2)	44 (42.3)	24 (59.9)	14 (70.1)	12 (78.8)	8 (84.7)	8 (90.5)	13 ^d (100)					
	MXF			2 ^c (1.5)	2 (2.9)	4 (5.8)	24 (23.4)	38 (51.1)	18 (64.2)	17 (76.6)	32^d (100)						
<i>S. maltophilia</i> (26)	NMX			1 (3.8)	1 (3.8)	6 (26.9)	4 (42.3)	8 (73.1)	2 (100)								
	CIP			1 ^c (3.8)	1 (3.8)	1 (3.8)	1 (3.8)	1 (3.8)	1 (3.8)	3 (80.8)	5^d (100)						
	LVX			1 ^c (3.8)	2 (7.7)	2 (15.4)	7 (42.3)	6 (65.4)	4 (92.3)	2 (100)							
	MXF																
<i>A. baumannii</i> (15)	NMX			4 (26.7)	7 (73.3)	2 (86.7)	1 (93.3)	1 (100)	1 (100)								
	CIP			2 (13.3)	6 (53.3)	4 (80)	1 (86.7)	1 (93.3)	1 (100)								
	LVX			5 (40)	6 (80)	1 (86.7)	1 (93.3)	1 (100)	1 (100)								
	MXF			6 ^c (40)	6 (80)	1 (86.7)	1 (93.3)	1 (100)	1 (100)								

^a FQ, fluoroquinolone; NMX, nemoxacin; CIP, ciprofloxacin; LVX, levofloxacin; MXF, moxifloxacin.^b The numbers of isolates and cumulative percentages for MIC₅₀ values are shown in boldface type.^c Lowest concentration tested. The actual MICs of some isolates may be lower than indicated.^d Highest concentration tested. The actual MICs of some isolates may be higher than indicated.

distributions and MIC_{90s}. Among the members of the family *Enterobacteriaceae*, nemonoxacin displayed activity similar to the activities of the other fluoroquinolones (nemonoxacin MIC_{90s}, 0.5 to 32 µg/ml; ciprofloxacin MIC_{90s}, ≤0.06 to ≥16 µg/ml; levofloxacin MIC_{90s}, ≤0.06 to 16 µg/ml; moxifloxacin MIC_{90s}, 0.12 to ≥16 µg/ml). Comparable activity between nemonoxacin and moxifloxacin was noted for *P. aeruginosa* (MIC_{90s}, ≥8 µg/ml), while nemonoxacin activity for *S. maltophilia* (MIC_{90s}, ≥4 µg/ml) was similar to levofloxacin activity. Similarly to levofloxacin and moxifloxacin, nemonoxacin displayed good activity against *A. baumannii* (MIC₉₀, 1 µg/ml).

On the basis of the free area under the concentration-time curve from 0 to 24 h (*fAUC*₀₋₂₄) achieved using a 750-mg dose of nemonoxacin in the community-acquired pneumonia trial (49.1 µg · h/ml; C. Richard King, TaiGen Biotechnology Co. Ltd., personal communication), favorable *fAUC*₀₋₂₄-to-MIC ratios (*fAUC*₀₋₂₄/MIC) are attainable with many of the organisms described in this study. The *fAUC*₀₋₂₄/MIC required to eradicate pathogens and prevent the emergence of resistance is dependent on the specific pathogen-quinolone combination, but it is generally accepted that *fAUC*₀₋₂₄/MICs of ≥100 to 125 are needed for gram-negative bacilli (17). Among the gram-positive cocci, ratios of <40 (but >30) have been established for *S. pneumoniae* (17). Accordingly, nemonoxacin displays good pharmacokinetics/pharmacodynamics at the 750-mg dose with *S. aureus* (*fAUC*₀₋₂₄/MIC, 393), CA-MRSA (*fAUC*₀₋₂₄/MIC, 98), *S. epidermidis* (*fAUC*₀₋₂₄/MIC, 98), and *S. pneumoniae*, including the penicillin-resistant isolates (*fAUC*₀₋₂₄/MIC, >393). Similar to other fluoroquinolones, on the basis of the MICs for some gram-negative bacilli in this study, *fAUC*₀₋₂₄/MICs of ≥100 to 125 would not be achieved with a nemonoxacin dose of 750 mg.

This study details the activity of nemonoxacin and other fluoroquinolones against a large collection of Canadian clinical isolates from the CANWARD 2007 surveillance program. Nemonoxacin displayed greater activity than the other fluoroquinolones against MSSA, MSSE, MRSE, *S. pneumoniae*, and *E. faecalis*. Nemonoxacin was more active than other fluoroquinolones versus MRSA. Interestingly, nemonoxacin maintained better activity against CA-MRSA than against HA-MRSA. Compared to CA-MRSA, the HA-MRSA isolates displayed greater resistance rates to all of the tested fluoroquinolones. The increase in the nemonoxacin MIC₉₀ against non-levofloxacin-susceptible *S. aureus* compared to levofloxacin-susceptible *S. aureus* indicates that the activity of nemonoxacin against *S. aureus* is related to the activity of the fluoroquinolone class, in general. The greater susceptibility of the currently circulating strains of CA-MRSA to the fluoroquinolone class compared to HA-MRSA may account for the stronger activity of nemonoxacin observed against CA-MRSA. However, as CA-MRSA isolates become increasingly resistant to other antimicrobial agents, including the fluoroquinolones, the activity of nemonoxacin may be adversely affected. Against the gram-negative bacilli, nemonoxacin was found to have activity comparable to those of levofloxacin and moxifloxacin.

At this time, fluoroquinolone-resistant isolates from the CANWARD study are not molecularly characterized. Accordingly, a limitation of this study is the lack of analysis of nemonoxacin activity against isolates with known quinolone resis-

tance-associated mutations. Future studies with characterized isolates are necessary.

The good activity of nemonoxacin against gram-positive and gram-negative organisms described herein suggests that further investigations with this novel C-8-methoxy nonfluorinated quinolone are warranted. In particular, the activity of nemonoxacin against gram-positive cocci should be studied further.

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