



Comparative Activity Of Gatifloxacin Against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* Before (1997-99) and During (2000) the Clinical Release in North America (NA): A SENTRY Antimicrobial Surveillance Program Report

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ABSTRACT

Purpose: To determine resistance trends in NA (United States [US], Canada [CA]) to gatifloxacin (GATI) and other contemporary fluoroquinolones (FQ) among commonly isolated respiratory tract pathogens from the 1997-1999 and 2000 SENTRY Antimicrobial Surveillance Program.

Methods: A total of 11,035 isolates were processed by a central monitor (Iowa) using the reference NCCLS method. The strain numbers tested were (1997-1999/2000): *H. influenzae* (HI; 3,271/1,194), *M. catarrhalis* (MCAT; 1,530/524) and *S. pneumoniae* (SPN; 3,363/1,103). The following drugs were tested and reported here: penicillin (PG), clarithromycin, erythromycin, ciprofloxacin (CIP), GATI, levofloxacin (LEVO) and trovafloxacin or moxifloxacin (T-M). Resistance demographics for this collection included: SPN PG intermediate / resistance (%) at 20/15 in 1997-1999 and 15/19 in 2000; β -lactamase rates in HI/MCAT at 28-31/95-96. Macrolide resistance increased significantly in SPN between the two monitored intervals.

Results: For HI and MCAT the β -lactamase-positive rates and FQ activities did not vary significantly between the two sample periods. Only rare single isolates with decreased FQ susceptibility were documented (0-2 strains/species). Among the FQ's, moxifloxacin was least potent against HI and MCAT (MIC₉₀ 0.12 mg/ml). For SPN, see the following trends:

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FQ	1997-1999 (n=3,367)		2000 (n=1,103)	
	MIC ₉₀	% Susc.	MIC ₉₀	% Susc.
CIP	1/2	(1.7) ^a	1/2	(3.5) ^a
LEVO	1/2	99.3	1/2	98.9
T-M	0.12/0.25	99.5	0.12/0.25	99.0
GATI	0.25/0.5	99.5	0.25/0.5	99.0

^a% of isolates MICs at >4 mg/ml (Chen et al. NEMJ, 1999), significant increase was observed in second sample interval (p < 0.05).

Conclusions: FQ resistances among common respiratory tract pathogens continues to evolve in NA, but was very rare among HI and MCAT. SPN LEVO resistance increased in the NA region (0.7 to 1.1%), and was related to a 2.0% (4 strains) rate in CA compared to stable rates in the US (0.9%; 8 strains) where newer FQ's have been introduced. GATI had the widest spectrum versus SPN in both nations.

INTRODUCTION

The newer fluoroquinolones such as gatifloxacin are emerging as highly desirable therapeutic agents for community-acquired respiratory tract infections. This change was fostered by the decline in the spectrum of orally administered β -lactams due to penicillin-resistance (altered PBP's) in *Streptococcus pneumoniae* and the production of various β -lactamases by *Haemophilus influenzae* and *Moraxella catarrhalis*. More recent increases in resistance rates to macrolides (azithromycin, clarithromycin, erythromycin) in all three cited species further compromises therapeutic choices. Gatifloxacin has potent activity against *S. pneumoniae* (MIC₉₀ 0.25 μ g/ml) and favorable pharmacokinetic features including once-daily dosing. This compound and moxifloxacin were introduced into clinical practice (United States [US]) in December, 1999. This study examines the resistance trends in North America for gatifloxacin and other contemporary fluoroquinolones among commonly isolated respiratory tract pathogens from 1997-1999 and 2000 e.g. before gatifloxacin introduction and the initial respiratory disease season. Only bacterial pathogens (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*) were assessed; atypical causes of community-acquired pneumonia were not sampled.

MATERIALS AND METHODS

A total of 11,035 isolates were processed by a central monitor (Iowa) using the reference NCCLS methods. The strain numbers tested were (1997-1999/2000): *H. influenzae* (HI; 3,271/1,194), *M. catarrhalis* (1,530/524) and *S. pneumoniae* (3,363/1,103). A total of 27 drugs were tested and some are reported here: penicillin (PG), clarithromycin, erythromycin, ciprofloxacin, gatifloxacin, levofloxacin and trovafloxacin or moxifloxacin. Resistance demographics for this collection included: pneumococcal intermediate/resistance rates (%) at 20/15 in 1997-1999 and 15/19 in 2000; β -lactamase rates in *H. influenzae* / *M. catarrhalis* at 28-31/95-96. Macrolide resistance increased significantly in the pneumococci between the two monitored intervals (Table 1).

TABLE 1: Significant resistance demographics of the organism collection tested by the SENTRY Program (North America only).

Organism / Parameter (No. Tested)	% By Years	
	1997 - 99	2000
<i>H. influenzae</i> (3,271/1,194)		
β -lactamase production	31.2	27.5
Clarithromycin susceptibility	78.7	85.4
<i>M. catarrhalis</i> (1,530/524)		
β -lactamase production	94.8	95.6
Erythromycin susceptibility	99.6	99.5
<i>S. pneumoniae</i> (3,363/1,103)		
Penicillin-intermediate	20.3	15.3
Penicillin-resistant	14.6	18.8
Erythromycin susceptibility	80.4	73.0 ^a

^aSignificant decline

TABLE 2: Comparisons of quinolone susceptibility testing data for 4,465 *H. influenzae* strains tested by the SENTRY Program from 1997-2000 (North American medical centers).

Quinolone	Years (No. Tested)							
	1997 - 99 (3,271)				2000 (1,194)			
	MIC ₅₀	MIC ₉₀	Range	% Susc. ^a	MIC ₅₀	MIC ₉₀	Range	% Susc. ^a
Gatifloxacin	≤ 0.03	≤ 0.03	$\leq 0.03-0.25$	100.0	≤ 0.03	≤ 0.03	$\leq 0.03-1$	99.9
Ciprofloxacin	≤ 0.016	≤ 0.016	$\leq 0.016-0.06$	100.0	≤ 0.016	≤ 0.016	$\leq 0.016-2$	99.9
Levofloxacin	≤ 0.03	≤ 0.03	$\leq 0.03-1$	100.0	≤ 0.03	≤ 0.03	$\leq 0.03-2$	100.0
Moxifloxacin	NT ^b	NT	NT	NT	≤ 0.03	≤ 0.03	$\leq 0.03-2$	99.9
Trovafloxacin	≤ 0.03	≤ 0.03	$\leq 0.03-4$	99.9	NT	NT	NT	NT

^aNCCLS criteria for susceptibility
^bNT = Not tested

TABLE 3: Comparisons of quinolone susceptibility testing results for 2,064 *M. catarrhalis* strains tested by the SENTRY Program from 1997-2000 (North American medical centers).

Quinolone	Years (No. Tested)							
	1997 - 99 (1,530)				2000 (524)			
	MIC ₅₀	MIC ₉₀	Range	% Susc. ^a	MIC ₅₀	MIC ₉₀	Range	% Susc. ^a
Gatifloxacin	≤ 0.03	≤ 0.03	$\leq 0.03-4$	99.9	≤ 0.03	≤ 0.03	$\leq 0.03-0.12$	100.0
Ciprofloxacin	≤ 0.016	≤ 0.016	$\leq 0.016-2$	99.9	≤ 0.016	≤ 0.016	$\leq 0.016-0.12$	100.0
Levofloxacin	≤ 0.03	≤ 0.03	$\leq 0.03-4$	99.9	≤ 0.03	≤ 0.03	$\leq 0.03-0.25$	100.0
Moxifloxacin	NT ^b	NT	NT	NT	0.12	0.12	$\leq 0.03-0.12$	100.0
Trovafloxacin	≤ 0.03	≤ 0.03	$\leq 0.03-4$	99.9	NT	NT	NT	NT

^aNCCLS criteria for susceptibility
^bNT = Not tested

TABLE 4: Comparisons of quinolone susceptibility testing results for 4,466 *S. pneumoniae* strains tested by the SENTRY Program from 1997-2000 (North American medical centers).

Quinolone	Years (No. Tested)							
	1997 - 99 (3,363)				2000 (1,103)			
	MIC ₅₀	MIC ₉₀	Range	% Susc. ^a	MIC ₅₀	MIC ₉₀	Range	% Susc. ^a
Ciprofloxacin	1	2	$\leq 0.016-2$	(1.7) ^a	1	2	$\leq 0.016-2$	(3.5) ^a
Gatifloxacin	0.25	0.5	$\leq 0.03-4$	99.5	0.25	0.5	$\leq 0.03-4$	99.0
Levofloxacin	1	2	$0.06-4$	99.3	1	1	$\leq 0.03-4$	98.9
Moxifloxacin	NT ^b	NT	NT	NT	0.12	0.25	$\leq 0.03-4$	99.0
Trovafloxacin	0.12	0.25	$\leq 0.03-4$	99.5	NT	NT	NT	NT

^aPercentage in parenthesis indicates proportion of isolates with a ciprofloxacin MIC at ≥ 4 μ g/ml (Chen et al., 1999).
^bNT = Not tested

RESULTS

- β -lactamase production rates were approximately one in three for *H. influenzae* and $> 90\%$ for *M. catarrhalis*, unchanged for more than five years.
- Very rare isolates of *H. influenzae* and *M. catarrhalis* have elevated fluoroquinolone MICs at a rate of 0 - 2 isolates per species/year. No increasing rate ($< 0.1\%$) was observed.
- Gatifloxacin MIC₉₀ (≤ 0.03 mg/ml) was stable for both Gram-negative species ($\geq 99.9\%$ susceptible isolates).
- Generally, an increase in quinolone-resistance in *S. pneumoniae* has been documented in North America from 1997 through 2000. Example: ciprofloxacin MICs at ≥ 4 mg/ml increased from 1.7% (1997-99) to 3.5% in 2000.
- Levofloxacin resistance was greater in 2000 (1.1%) than in the benchmark years of 1997-99 (0.7%) for *S. pneumoniae*.
- Gatifloxacin, moxifloxacin (2000 only) and trovafloxacin (1997-99 only) had slightly wider spectrums (99.0%) compared to levofloxacin when tested against *S. pneumoniae*.
- Approximately two-fold differences in quinolone resistance rates in *S. pneumoniae* were observed between the US and Canada in 2000: US at 0.9% and Canada at 2.0% for levofloxacin (12 strains overall).

CONCLUSIONS

- Gatifloxacin sustained the widest overall spectrum against the three monitored respiratory tract pathogens into the first year of clinical use, slightly greater than levofloxacin and equal to moxifloxacin.
- Quinolone-resistant *H. influenzae* and *M. catarrhalis* strains remain very rare and sporadic in occurrence.
- S. pneumoniae* isolates resistant to levofloxacin and other quinolones are also rare (approximately 1%) but appear to be increasing with a geographically differing pattern in North America (Canada > US) that maybe related to usage statistics. Further surveillance efforts appear prudent.

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