In vitro Activity of Delafloxacin Against *Neisseria gonorrhoeae* Clinical Isolates

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Introduction

Neisseria gonorrhoeae has plagued humans for centuries, and even today it is the second most reported notifiable infectious disease in the US, with more than 300,000 cases in 2011 alone (1). Spread via sexual contact, the range of infections caused by *N. gonorrhoeae* is wide: urethritis, cervicitis, pharyngitis, pelvic inflammatory disease; however, in many cases, particularly cervical, pharyngeal and rectal infections, the disease is asymptomatic. Left untreated, gonorrhea can lead to serious reproductive issues in women, not only pelvic inflammatory disease, but also ectopic pregnancy and infertility; in addition, there is the more dire concern that such cases can also facilitate HIV transmission (1). Currently, gonorrhea is treated with empiric antimicrobial therapy, as susceptibility testing is not routinely available in US clinics (1, 2). As such there is a pressing need for an agent(s) that can be safely administered as a single dose in the community setting.

The growing resistance of *N. gonorrhoeae* to antibiotics is a cascading story that has accelerated over the past 70 years. Early antibiotics such as sulfonamides and penicillin were very effective against this organism; however, resistance has obliterated their curative abilities. The Gonococcal Isolate Surveillance System (GISP) was started by the CDC in 1986 in order to monitor gonococcal antimicrobial susceptibility. Eventually tetracycline also lost its effectiveness against this organism, and during the 1990s and 2000s, fluoroquinolone-resistant *N. gonorrhoeae* (QRNG) emerged (1, 2, 3, 4). Their rapid spread led to QRNG rising to >5% of *N. gonorrhoeae* isolates in the US; as such, as of 2007 fluoroquinolones could no longer be recommended for treating gonorrhea (3), falling short of the recognized standard of a >95% effectiveness rate. Only the cephalosporins are recommended for anti-gonococcal therapy (1, 2). The current treatment regimen, 250 mg of ceftriaxone dosed IM plus either oral azithromycin or tetracycline (to treat *Chlamydia trachomatis*, a frequently-occurring co-pathogen) has been effective, but the increase in ceftriaxone-resistant organisms in the last decade has underscored the need for new agents to treat this infection. The purpose of this study was to determine whether the investigational fluoroquinolone, delafloxacin, has the anti-gonoccocal activity to warrant clinical evaluation.

Methods

Delafloxacin and other antimicrobial agents were evaluated for their *in vitro* activity against isolates of *N. gonorrhoeae* in two separate studies conducted in the laboratory of M. Roberts (Study A, n=113) and at CDC (Study B, n=93). MICs for delafloxacin and comparator compounds were determined by CLSI agar dilution methodology (8, 9). In Study A, 33.6% of the isolates were CIP-R and 29.3% of the isolates were multidrug-resistant (MDR). In Study B, 73.1% of the isolates were CIP-R, whereas 44.4% were MDR. Results are reported as µg/mL. Also included in Study A were ten control strains with identified resistance to penicillin, tetracycline, erythromycin, and fluoroquinolones; in study B five CDC-control strains were used (CDC-10328, CDC-10329, F-28, SPJ-15 and SPL-4), which tested intermediate resistance to ciprofloxacin, resistance to ciprofloxacin, spectinomycin resistance, decreased susceptibility to azithromycin and decreased susceptibility to cefixime, respectively. Comparator compounds in both studies included ciprofloxacin, ceftriaxone, spectinomycin, penicillin, and tetracycline. Study A also assessed the activity of erythromycin, while study B included ofloxacin, azithromycin, cefoxitin, cefixime, and cefpodoxime.

Results

In Study A, delafloxacin and control antibiotics were tested against 10 isolates with defined resistance mechanisms and 113 *N. gonorrhoeae* isolates from across the US, isolated in 2005. Within this set, all isolates were susceptible to spectinomycin and all but 7 were penicillin-resistant, and all but 14 were tetracycline-resistant (either intermediate or resistant). In addition, 33.6% were resistant to ciprofloxacin and ~10% had elevated MICs to erythromycin. Forty of these isolates were MDR, with resistance to penicillin, spectinomycin and ciprofloxacin, and 39/40 isolates were also tetracycline-resistant.

Delafloxacin demonstrated potent antimicrobial activity against *N. gonorrhoeae* isolates, including MDR strains. MICs for delafloxacin vs. CIP-R isolates were extremely potent, with generally >32-fold lower values than those of ciprofloxacin, and with similar potency as ceftriaxone. In the two studies, the MIC_{90}s for delafloxacin were 0.06 (A) and 0.125 (B) µg/mL, respectively; the MIC_{100}s were 0.125 (A) and 0.5 (B), respectively.

Table 1 shows the MICs for delafloxacin and control antibiotics; of note the MIC values do not change if the 10 control strains are included except that the range of penicillin MICs is broadened to 32 µg/mL.

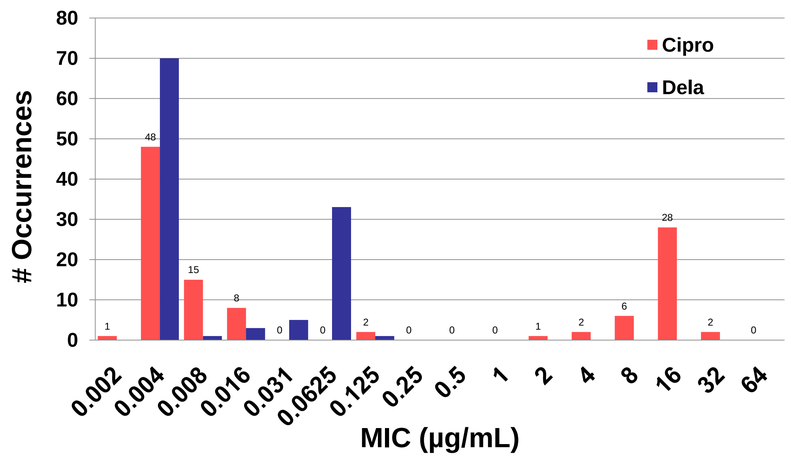
Table 1. Delafloxacin demonstrates potency against *N. gonorrhoeae.* Study A (n=113); MIC values in µg/mL

Agent	Range	MIC_{50}	MIC_{90}
Delafloxacin	0.004 – 0.125	0.004	0.06
Ciprofloxacin	0.004 – 32	0.008	16
Spectinomycin	<128	<128	<128
Ceftriaxone	0.001 – 0.06	0.008	0.03
Erythromycin	0.125 – 16	0.5	2
Penicillin	0.03 – 4	0.5	2
Tetracycline	0.06 – 32	1	2

Results

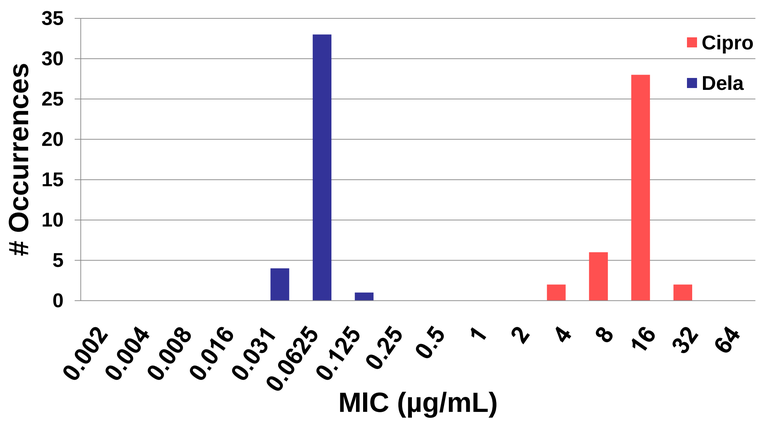
Against 113 isolates of *N. gonorrhoeae* tested in Study A, delafloxacin and ceftriaxone were the most potent antimicrobial agents with MIC_{90}s of 0.06 and 0.03 µg/mL, respectively. Delafloxacin was more than 250 times more active than ciprofloxacin against these isolates.

Figure 1. MIC distributions of Fluoroquinolones Against *N. gonorrhoeae* in Study A (N=113)



In this collection of *N. gonorrhoeae* from Study A, 38 of 113 isolates were CIP-R (CIP MICs of ≥1 µg/mL), with delafloxacin MICs of 0.03-0.125 µg/mL. Figure 2 focuses on these isolates, emphasizing the robustness of delafloxacin in the face of quinolone resistance. It should be mentioned that the quinolone-resistant CDC control strain (CDC-10329) was included in this panel. The MICs against CDC-10329 were 2 and 0.0625 µg/mL for ciprofloxacin and delafloxacin, respectively.

Figure 2. MIC distributions of Fluoroquinolones Against Cipro-resistant *N. gonorrhoeae* in Study A (N=38)



Study B evaluated the *in vitro* antimicrobial activity of 11 agents against 93 isolates of *N. gonorrhoeae* (Table 2) plus the CDC-control strains. Delafloxacin and several cephalosporins demonstrated robust activity against this group of organisms, with MIC_{90}s of 0.06-0.25 µg/mL. In this study as well, delafloxacin's MIC_{90} was >250-fold lower than that of ciprofloxacin.

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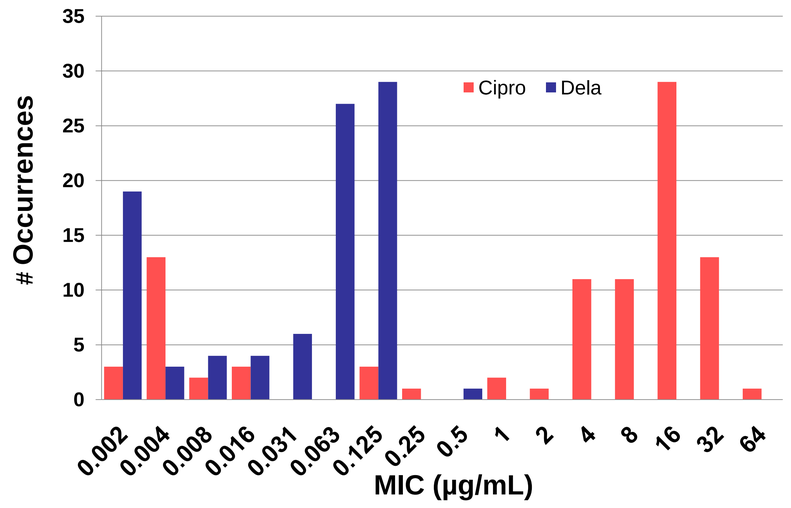
Table 2. Delafloxacin demonstrates potency against *N. gonorrhoeae.* Study B (n=93); MIC values in µg/mL

Agent	Range	MIC_{50}	MIC_{90}
Delafloxacin	≤0.002-0.5	0.06	0.125
Ciprofloxacin	≤0.002-64	8.0	32.0
Ofloxacin	≤0.002-64	16.0	16.0
Azithromycin	≤0.03->4	0.25	4.0
Spectinomycin	≤256.0->256	≤256.0	≤256.0
Ceftriaxone	≤0.001-0.125	0.008	0.06
Cefoxitin	0.5->8	4.0	4.0
Cefixime	0.002->1	0.03	0.125
Cefpodoxime	≤0.008-4	0.125	0.25
Penicillin	0.015->64	2.0	8.0
Tetracycline	0.06->32	1.0	4.0

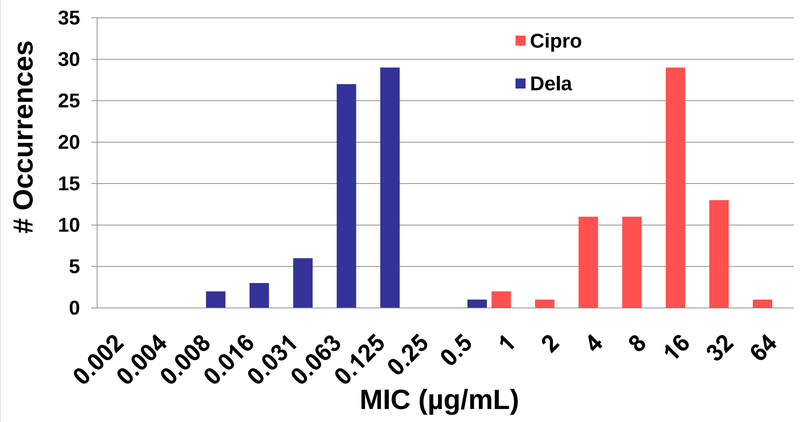
Figure 3 shows the relative performances of delafloxacin and ciprofloxacin in Study B. MICs for the CIP-S isolates were extremely potent, with a range of ≤0.002-0.004 µg/mL.

Figure 3. MIC distributions of Fluoroquinolones Against *N. gonorrhoeae* in Study B (N=93)



Results

Figure 4. MIC distributions of Fluoroquinolones Against Cipro-resistant *N. gonorrhoeae* in Study B (N=68)



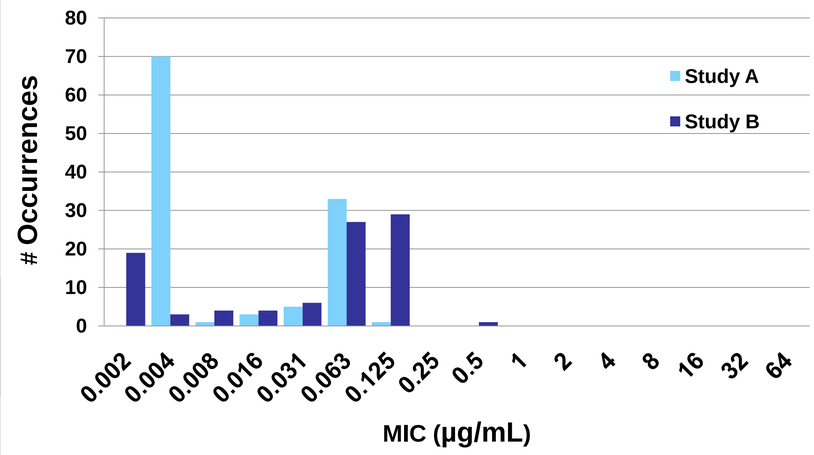
Of the 93 isolates in Study B, 73.1% were resistant to ciprofloxacin. Figure 4 focuses on these isolates. Delafloxacin MICs for this CIP-R group were 0.008-0.5 µg/mL, significantly lower than those for ciprofloxacin. Against all isolates of *N. gonorrhoeae* tested in these studies (Table 3), delafloxacin and ceftriaxone were the most active antimicrobial agents. The MIC_{90} of delafloxacin was 128-fold lower than that of ciprofloxacin in these combined studies.

Table 3. Delafloxacin demonstrates potent activity against *N. gonorrhoeae.* Combined Study A and Study B (n=206); MIC values in µg/mL

Agent	Range	MIC_{50}	MIC_{90}
Delafloxacin	≤0.002-0.5	0.015	0.125
Ciprofloxacin	≤0.002-64	2	16
Spectinomycin	≤256.0->256	≤256.0	≤256.0
Ceftriaxone	≤0.001-0.125	0.008	0.03
Penicillin	0.015->64	1	4
Tetracycline	0.06->32	1	2

Figure 5 shows the relative performance of delafloxacin in Studies A and B. Despite the increase in resistance to ciprofloxacin from 2005 to 2010, delafloxacin activity remains robust.

Figure 5. Comparison of MIC distributions of Delafloxacin in both studies of *N. gonorrhoeae*



Conclusions

1. Delafloxacin exhibits excellent *in vitro* antimicrobial activity against *N. gonorrhoeae*, including ciprofloxacin-resistant isolates.

2. Delafloxacin demonstrates potency similar to that of ceftriaxone against *N. gonorrhoeae*.

3. In consideration of the diminishing available treatment options for gonorrhea, further investigation of delafloxacin is warranted.

4. Delafloxacin's robust activity against *N. gonorrhoeae* is consistent between studies performed in 2007 and 2010.

References

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