

In Vitro Activity of Delafloxacin Tested against Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis

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ABSTRACT

Background: Delafloxacin (DLX) is a broad spectrum fluoroquinolone in late stage clinical development in both oral and intravenous formulations. The in vitro activity of DLX was evaluated against contemporary (USA; 2014) Streptococcus pneumoniae (SPN), Haemophilus influenzae (HIN), and Moraxella catarrhalis (MC) isolates.

Methods: A total of 200 SPN, 200 HIN and 100 MC isolates from a broad geographic distribution across the USA (2014) were tested by MIC against DLX and comparators. Also, a collection of 30 levofloxacin (LEV)-resistant SPN from the USA and Europe were tested. MC were tested in cation-adjusted Mueller-Hinton broth (CA-MHB); SPN in CA-MHB supplemented with lysed horse blood (2.5-5%); and HIN in Haemophilus Test Medium (HTM). Clinical and Laboratory Standards Institute quality control ranges and interpretive criteria were applied.

Results: The DLX MIC50 and MIC90 for SPN was 0.008 and 0.015 µg/mL, respectively. DLX was 128 x (MIC50) and 64 x (MIC90) more active than LEV. Susceptibility (S) to a number of antimicrobials was compromised for SPN (erythromycin, 52.5% S; trimethoprim-sulfamethoxazole, 75.5% S; tetracycline, 81.0% S; meropenem; 86.0% S). The MIC50 and MIC90 for DLX and LEV were unchanged for the penicillin-susceptible, -intermediate, or -resistant subsets of SPN. DLX was 16 x more active than the next potent comparator, ceftaroline (MIC90, 0.015 versus 0.25 µg/mL) against penicillin-resistant isolates. DLX (MIC50 and MIC90, 0.12 and 0.5 µg/mL) was active against the collection of LEV-resistant SPN. Ceftaroline (MIC90, 0.12 µg/mL; 100.0% S) exhibited the most potent activity against LEV-resistant SPN. For HIN, 24% of which were beta-lactamase positive, the MIC50 and MIC90 values for DLX were ≤0.001 and 0.004 µg/mL. The activities of DLX and LEV against HIN were unaffected by beta-lactamase status. Both DLX and LEV were active against MC (95% beta-lactamase positive). DLX was the most potent agent tested against MC.

Conclusions: DLX was active against penicillin-resistant, ceftriaxone non-susceptible and LEV-resistant subsets of SPN. The potent in vitro activity of DLX against pathogens frequently associated with community-acquired pneumonia (SPN, HIN and MC), including those that are multidrug-resistant indicate that further study in community-acquired pneumonia is warranted.

INTRODUCTION

Delafloxacin is active against a broad range of Gram-positive and Gram-negative bacteria including anaerobes and atypical bacteria (Chlamydia and Mycoplasma). It has been shown to be highly active against pathogens which are found in skin and soft tissue infections including fluoroquinolone resistant staphylococci (methicillin-resistant Staphylococcus aureus and methicillin-resistant coagulase-negative staphylococci), beta-hemolytic streptococci, Enterobacteriaceae, Pseudomonas aeruginosa, and anaerobes. Delafloxacin is also active against bacteria associated with respiratory tract infections (hospital and community-acquired respiratory infections) including activity against fluoroquinolone resistant Streptococcus pneumoniae.

The aim of this study was to examine the activity profile of delafloxacin against contemporary S. pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis clinical isolates collected primarily from United States medical centers during 2014.

MATERIALS AND METHODS

Susceptibility testing: MIC values were determined for S. pneumoniae and H. influenzae using the reference CLSI broth microdilution method as described in M07-A10 [2015]; broth microdilution for M. catarrhalis as described in M45-A2 [2010]. Dry-form panels manufactured by Thermo Fisher Scientific Inc. (Cleveland, Ohio, USA) were used and consisted of three media types: cation-adjusted Mueller-Hinton broth (CA-MHB), Haemophilus Test Medium (HTM), and CA-MHB plus 2.5-5.0% lysed horse blood. Frozen-form panels were produced at JMI Laboratories to test delafloxacin, levofloxacin and ciprofloxacin against H. influenzae and M. catarrhalis isolates. Interpretive criteria for comparator antimicrobials were those as published by CLSI (M100-S25; 2015) and EUCAST (2015). Quality control was performed per CLSI M07-A10 [2015] and CLSI M100-S25 [2015] recommendations and guidelines and included S. aureus ATCC 29213, S. pneumoniae ATCC 49619, and H. influenzae ATCC 49247.

Organism collection: A total of 200 S. pneumoniae, 200 H. influenzae, and 100 M. catarrhalis from a broad geographic distribution in the USA (2014) were selected. In addition, 30 levofloxacin-resistant S. pneumoniae isolates from 2014 (20 from USA, 9 from Europe and one from Australia) were selected.

RESULTS

The MIC distributions for delafloxacin tested against 200 contemporary S. pneumoniae, 200 H. influenzae, and 100 M. catarrhalis (2014; geographically diverse from across the USA census regions) and a collection of 30 levofloxacin-resistant S. pneumoniae isolates (20 from USA, 9 from Europe and one from Australia; all from 2014) are located in Table 1.

Streptococcus pneumoniae

- The delafloxacin MIC50 and MIC90 against S. pneumoniae were 0.008 and 0.015 µg/mL, respectively (Table 1). Delafloxacin was 128 (MIC50) and 64-fold (MIC90) more active than levofloxacin against the 200 S. pneumoniae (Table 2). The highest delafloxacin MIC was 0.12 µg/mL (Table 2). The levofloxacin MIC50 and MIC90 was 1 and 1 µg/mL, respectively (Table 2). The MIC50 and MIC90 for delafloxacin (0.008 and 0.015 µg/mL, respectively) and levofloxacin (1 and 1 µg/mL, respectively) were unchanged for the penicillin-susceptible, -intermediate, or -resistant subsets of S. pneumoniae (Table 1).

- The activity of delafloxacin and levofloxacin was retained against nine ceftriaxone non-susceptible isolates (Table 2). The highest MIC for delafloxacin was 0.015 µg/mL and for levofloxacin was 2 µg/mL (Table 2).

- Delafloxacin (MIC50 and MIC90, 0.12 and 0.5 µg/mL, respectively) was active against the collection of levofloxacin-resistant S. pneumoniae (Tables 1, 2). MIC values for delafloxacin were increased 16- to 32-fold relative to the general population of S. pneumoniae (Table 1).
- Delafloxacin was the most active agent tested against S. pneumoniae (Table 2). It was 8-fold more potent than the next most potent agent, ceftaroline (MIC90, 0.12 µg/mL; 100.0% susceptible), against the collection of contemporary, geographically diverse S. pneumoniae isolates (Table 2). Susceptibility to a number of antimicrobials was compromised (erythromycin, 52.5% susceptible; trimethoprim-sulfamethoxazole, 75.5% susceptible; tetracycline, 81.0% susceptible; meropenem; 86.0% susceptible).

Penicillin-resistant S. pneumoniae

- Delafloxacin was 16-fold more active than the next potent agent, ceftaroline (MIC90, 0.015 versus 0.25 µg/mL) against penicillin-resistant isolates (Table 2). Susceptibility for most antimicrobials was generally decreased in this subgroup (penicillin-resistant) compared to the general population with the exception of the fluoroquinolones and ceftaroline. For example, susceptibility to erythromycin, trimethoprim-sulfamethoxazole, and ceftriaxone were 7.7, 15.4 and 53.8%, respectively.

Ceftriaxone non-susceptible S. pneumoniae

- The highest MIC for delafloxacin was 16-fold lower than for the most potent comparator moxifloxacin (0.015 versus 0.25 µg/mL; 100.0% susceptible) and 32-fold lower than for ceftaroline (0.015 versus 0.5 µg/mL; 100.0% susceptible) against ceftriaxone non-susceptible S. pneumoniae (Table 2). The fluoroquinolones (levofloxacin and moxifloxacin) and ceftaroline retained activity (100.0% susceptible), however many of the antimicrobials showed decreased activity compared to the overall population.

Levofloxacin-resistant S. pneumoniae

- Ceftaroline (MIC90, 0.12 µg/mL; 100.0% susceptible) demonstrated the most potent activity against levofloxacin-resistant S. pneumoniae (Table 2). Delafloxacin was the next most active agent (MIC90, 0.5 µg/mL) followed by meropenem (MIC90, 1 µg/mL; 66.7% susceptible) and ceftriaxone (MIC90, 2 µg/mL; 83.3% susceptible). Limited activity with moxifloxacin was noted (MIC90, 4 µg/mL; 20.0% susceptible; Table 2).

Haemophilus influenzae

- Delafloxacin and levofloxacin were active against 200 contemporary H. influenzae (2014; geographically diverse from across USA census regions), 24% of which were beta-lactamase positive (Table 3). The MIC50 and MIC90 values for delafloxacin were ≤0.001 and 0.004 µg/mL, respectively (highest MIC value at 0.25 µg/mL). For levofloxacin the MIC50 and MIC90 values were 0.015 and 0.03 µg/mL, respectively. However for levofloxacin there were two isolates that were not susceptible (MIC, >2 µg/mL).

- The activities of delafloxacin and levofloxacin against H. influenzae were unaffected by beta-lactamase status (Table 1).

Table 1. Cumulative frequency distribution of delafloxacin MIC results when tested against S. pneumoniae, H. influenzae, and M. catarrhalis isolates.

Table with 11 columns: Organism (no. tested), No. of organisms (cumulative %) inhibited at delafloxacin MIC in µg/mL of: ≤0.001, 0.002, 0.004, 0.008, 0.015, 0.03, 0.06, 0.12, 0.25, 0.5, 1, MIC50, MIC90. Rows include Streptococcus pneumoniae (200), Pen-S, Pen-I, Pen-R, CRO-non-S, Levofloxacin-R, H. influenzae (200), beta-lactamase-positive (48), and M. catarrhalis (100).

- Delafloxacin was the most potent agent tested against H. influenzae (Table 3). The MIC90 (0.004 µg/mL) for delafloxacin was 4- and 8-fold lower than for ciprofloxacin and levofloxacin, respectively (Table 3). Ciprofloxacin and levofloxacin susceptibilities were 99.0% and all isolates were susceptible to ceftaroline, ceftazidime and meropenem. Tetracycline (93.8% compared to 100.0% for beta-lactamase-negative isolates) and trimethoprim-sulfamethoxazole (62.5% compared to 65.8%) susceptibilities were lower for the beta-lactamase-positive isolates (data not shown).

Moraxella catarrhalis

- Delafloxacin, levofloxacin and ciprofloxacin were active against M. catarrhalis (95% beta-lactamase positive). However, delafloxacin was 8-fold more active than levofloxacin and ciprofloxacin (Table 3).
- Delafloxacin was the most potent agent tested against M. catarrhalis (Table 3). All isolates were susceptible to amoxicillin-clavulanate, ceftazidime, ciprofloxacin, levofloxacin, and tetracycline.

Table 3. Activity of delafloxacin and comparator antimicrobial agents when tested against isolates of H. influenzae and M. catarrhalis.

Table with 6 columns: Organism group (no. tested)/ antimicrobial agent, MIC50, MIC90, Range, CLSI%, EUCAST%. Rows include Haemophilus influenzae (200), M. catarrhalis (100), and a comparison table for S. pneumoniae (2015) and EUCAST (2015) MIC breakpoints.

Table with 11 columns: Organism (no. tested), No. of organisms (cumulative %) inhibited at delafloxacin MIC in µg/mL of: ≤0.001, 0.002, 0.004, 0.008, 0.015, 0.03, 0.06, 0.12, 0.25, 0.5, 1, MIC50, MIC90. Rows include Streptococcus pneumoniae (200), Pen-S, Pen-I, Pen-R, CRO-non-S, Levofloxacin-R, H. influenzae (200), beta-lactamase-positive (48), and M. catarrhalis (100).

Table 2. Activity of delafloxacin and comparator antimicrobial agents when tested against Streptococcus pneumoniae.

Table with 6 columns: Organism group (no. tested)/ antimicrobial agent, MIC50, MIC90, Range, CLSI%, EUCAST%. Rows include Streptococcus pneumoniae (200), Penicillin-resistant (MIC, ≥2 µg/mL; 13), Ceftriaxone-non-susceptible (MIC, ≥2 µg/mL; 9), and Levofloxacin-R (MIC, ≥8 µg/mL; 30).

CONCLUSIONS

- Delafloxacin was the most potent compound tested against S. pneumoniae, H. influenzae and M. catarrhalis. It was 64- to 128-fold more potent than levofloxacin against S. pneumoniae and 8-fold more potent against H. influenzae and M. catarrhalis.
- Delafloxacin was active against penicillin-resistant, ceftriaxone non-susceptible and levofloxacin-resistant subsets of S. pneumoniae.
- Delafloxacin activity was not affected by beta-lactamase status for H. influenzae and M. catarrhalis.
- The potent activity of delafloxacin, particularly against multi-drug resistant pathogens, demonstrates that further clinical study in community-acquired pneumonia are warranted.

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REFERENCES

1. Almer LS, Hoffrage JB, Keller EL, Flamm RK, Shortridge VD (2004). In vitro and bactericidal activities of ABT-492, a novel fluoroquinolone, against Gram-positive and Gram-negative organisms. Antimicrob Agents Chemother 48: 2771-2777.
2. Clinical and Laboratory Standards Institute (2015). M07-A10. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard- tenth edition. Wayne, PA: CLSI.
3. Clinical and Laboratory Standards Institute (2015). M100-S25. Performance standards for antimicrobial susceptibility testing: 25th informational supplement. Wayne, PA: CLSI.
4. Clinical and Laboratory Standards Institute (2010). M45-A2. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria: second edition. Wayne, PA: CLSI.
5. EUCAST (2015). Breakpoint tables for interpretation of MICs and zone diameters. Version 5.0, January 2015. Available at: http://www.eucast.org/clinical_breakpoints/. Accessed January 2015.
6. Goldstein EJ, Citron DM, Merriam CV, Warren YA, Tyrrell KL, Fernandez HT (2003). In vitro activities of ABT-492, a new fluoroquinolone, against 155 aerobic and 171 anaerobic pathogens isolated from antral sinus puncture specimens from patients with sinusitis. Antimicrob Agents Chemother 47: 3008-3011.
7. Niluis AM, Shen LL, Hensey-Rudloff D, Almer LS, Beyer JM, Balli DJ, Cai Y, Flamm RK (2003). In vitro antibacterial potency and spectrum of ABT-492, a new fluoroquinolone. Antimicrob Agents Chemother 47: 3260-3269.
8. O'Riordan W, Mehra P, Manos P, Kingsley J, Lawrence L, Cammarata S (2015). A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. Int J Infect Dis 30: 67-73.
9. Remy JM, Tow-Keogh CA, McConnell TS, Dalton JM, Devito JA (2012). Activity of delafloxacin against methicillin-resistant Staphylococcus aureus: resistance selection and characterization. J Antimicrob Chemother 67: 2814-2820.
10. Waites KB, Crabb DM, Duffy LB (2003). Comparative in vitro susceptibilities and bactericidal activities of investigational fluoroquinolone ABT-492 and other antimicrobial agents against human mycoplasmas and ureaplasmas. Antimicrob Agents Chemother 47: 3973-3975.