

# Enhanced Activity of Sitafloxacin against a Large Collection of Gram-positive Isolates From Latin America

The JONES Group/JMI Laboratories  
North Liberty, IA, USA  
www.jmilabs.com  
319.665.3370, fax 319.665.3371  
ronald-jones@jmilabs.com

SS ANDRADE, AC GALES, RN JONES, LC MENEZES, HS SADER

Universidade Federal de Sao Paulo, Sao Paulo, Brazil, The Jones Group/JMI Laboratories, North Liberty, IA.

E-163

I  
C  
C  
A  
C

2

0

0

0

3

## AMENDED ABSTRACT

**Background:** Sitafloxacin (SIT) is a fluoroquinolone with a broad spectrum of activity and highly potent against staphylococci, streptococci, and enterococci. Previous studies have demonstrated the activity of SIT against these bacteria, but it has not yet been confirmed with collaborative studies in Latin America (LA).

**Methods:** A total of 707 Gram-positive isolates were collected and tested against SIT in a central laboratory using NCCLS methods. The SIT activity was compared to gatifloxacin (GAT), garenoxacin (GRN) and levofloxacin (LEV).

**Results:** MIC<sub>90</sub>s of important Gram-positive pathogens were determined as follows:

| Organism                                       | MIC <sub>90</sub> (µg/mL) |              |              |             |
|--|---------------------------|--------------|--------------|-------------|
|  | Sitafloxacin              | Gatifloxacin | Levofloxacin | Garenoxacin |
| Oxacillin-resistant <i>S. aureus</i> (n=134)   | 1                         | 4            | > 4          | 2           |
| Oxacillin-susceptible <i>S. aureus</i> (n=160) | 0.03                      | 0.12         | 0.25         | 0.03        |
| Oxacillin-resistant CoNS (n=116)               | 0.25                      | 2            | > 4          | 2           |
| Oxacillin-susceptible CoNS (n=21)              | 0.03                      | 0.12         | 0.25         | 0.06        |
| <i>S. pneumoniae</i> (n=206)                   | 0.06                      | 0.25         | 1            | 0.06        |
| viridans group streptococci (n=18)             | 0.03                      | 0.5          | 1            | 0.12        |
| <i>Enterococcus</i> spp. (n=54)                | 2                         | > 4          | > 4          | 4           |

SIT showed higher activity than GAT, GRN and LEV against oxacillin-resistant staphylococci and *Enterococcus* spp. Against *S. pneumoniae*, a convergence of activity was noticed among SIT and GRN. However, SIT activity was greater than that of LEV and GAT for tested *S. pneumoniae* from LA.

**Conclusions:** SIT demonstrated excellent antimicrobial activity against a large collection of Gram-positive isolates from LA institutions, and proved to be superior to GRN, GAT and LEV for certain selected specimens.

## INTRODUCTION

Sitafloxacin (formely DU-6859a) is a newer fluoroquinolone with a broad spectrum of activity including staphylococci, streptococci, Enterobacteriaceae and anaerobes. Sitafloxacin has demonstrated broader spectrum and higher potency against Gram-positive and Gram-negative bacteria than currently marketed quinolones.

In the present study, the in vitro activity of sitafloxacin against recent clinical isolates collected in Latin American medical centers was investigated and compared with the activities of other quinolones.

## MATERIALS & METHODS

**Organisms:** Clinical isolates of aerobic bacteria were consecutively collected in microbiology laboratories located in Brazil, Argentina, Chile, and Venezuela. The participant medical centers were directed by a protocol to collect isolates from consecutive patients from specific sites of infections. A total of 707 clinical bacterial isolates collected from the Latin American region in the year 2002 were evaluated.

**Susceptibility testing:** Antimicrobial susceptibility testing was performed using broth microdilution methods as described by the National Committee for Clinical Laboratory Standards (NCCLS). Antimicrobial agents were obtained from their respective manufacturer as laboratory grade powder. MIC results were interpreted according to NCCLS breakpoints. Quality control of test procedures and reagents was monitored throughout routine testing *Streptococcus pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853.

## COMMENTS

- The largest number of isolates was collected in Brazil (362, 51.2%), followed by Argentina (167, 23.6%), Chile (147, 20.8%), and Venezuela (31, 4.4%; Table 1).
- Sitafloxacin showed excellent in vitro activity against oxacillin-susceptible *S. aureus* (OSSA; MIC<sub>50</sub>, 0.015 µg/ml and MIC<sub>90</sub>, 0.03 µg/ml). Sitafloxacin was 16-fold more potent than ciprofloxacin (MIC<sub>50</sub>, 0.25 µg/ml) and 8-fold more potent than levofloxacin (MIC<sub>50</sub>, 0.12 µg/ml) against OSSA strains (Tables 2 and 3).
- Sitafloxacin was very active against oxacillin-resistant *S. aureus* (ORSA; MIC<sub>50</sub>, 0.25 µg/ml and MIC<sub>90</sub>, 1 µg/ml; Tables 2 and 3).
- Sitafloxacin was also highly active against both oxacillin-susceptible and -resistant CoNS (MIC<sub>90</sub>, 0.03 and 0.25 µg/ml respectively).
- Sitafloxacin and garenoxacin were the most active compounds tested against *S. pneumoniae* (MIC<sub>50</sub>, 0.03 µg/ml and MIC<sub>90</sub>, 0.06 µg/ml for both compounds). These compounds were 32-fold more potent than levofloxacin (MIC<sub>50</sub>, 1 µg/ml) and 8-fold more potent than gatifloxacin (MIC<sub>50</sub>, 0.25 µg/ml) against this pathogen (Table 3).
- Viridans group streptococci was highly susceptible to sitafloxacin with all isolates tested being inhibited at ≤0.12 µg/ml (Table 2).
- Enterococcus* spp. strains showed the highest MICs for all quinolones tested. This pathogen presented a bi-modal distribution of sitafloxacin MICs with 25% of strains showing MIC ≤1 µg/ml (Table 2).

## RESULTS

**Table 1.** Distribution of major Gram-positive pathogens tested for sitafloxacin according to the country of isolation.

| Organism                        | Country (total number of isolates) |        |       |           | Total |
|---------------------------------|------------------------------------|--------|-------|-----------|-------|
|                                 | Argentina                          | Brazil | Chile | Venezuela |       |
| <i>S. aureus</i>                |                                    |        |       |           |       |
| oxacillin-susceptible           | 32                                 | 87     | 31    | 10        | 160   |
| oxacillin-resistant             | 30                                 | 67     | 35    | 2         | 134   |
| CoNS <sup>a</sup>               |                                    |        |       |           |       |
| oxacillin-susceptible           | 5                                  | 14     | -     | 2         | 21    |
| oxacillin-resistant             | 23                                 | 81     | 5     | 7         | 116   |
| <i>Streptococcus pneumoniae</i> | 64                                 | 75     | 60    | 7         | 206   |
| Viridans group streptococci     | 2                                  | 6      | 9     | 1         | 18    |
| <i>Enterococcus</i> spp.        | 11                                 | 32     | 7     | 2         | 52    |
| Total                           | 167                                | 362    | 147   | 31        | 707   |

a. CoNS: Coagulase-negative staphylococci.

**Table 2.** Distribution of MICs for sitafloxacin against 707 Gram-positive pathogens from Latin America.

| Organism (n tested)              | No. of isolates (cumulative %) inhibited at MIC (µg/ml) of: |          |          |           |          |          |          |          |          |         |        |
|----------------------------------|---|----------|----------|-----------|----------|----------|----------|----------|----------|---------|--------|
|                                  | ≤0.004  | 0.008    | 0.015    | 0.03      | 0.06     | 0.12     | 0.25     | 0.5      | 1        | 2       | 4      |
| <i>S. aureus</i>                 |   |          |          |           |          |          |          |          |          |         |        |
| Oxacillin-susceptible (160)      | 3 (1.9)   | 53(35.0) | 80(85.0) | 22(98.8)  | 1(99.4)  | -        | 1(100)   | -        | -        | -       | -      |
| Oxacillin-resistant (134)        | -   | 4(3.0)   | 3(5.2)   | -         | -        | 5(9.0)   | 75(64.9) | 28(85.8) | 16(97.8) | 3(100)  | -      |
| CoNS <sup>a</sup>                |   |          |          |           |          |          |          |          |          |         |        |
| Oxacillin-susceptible (21)       | -   | 1(4.8)   | 15(76.2) | 5(100)    | -        | -        | -        | -        | -        | -       | -      |
| Oxacillin-resistant(116)         | 4(3.4)  | 5(7.8)   | 37(39.7) | 9(47.4)   | 6(52.6)  | 29(77.6) | 18(93.1) | 7(99.1)  | 1(100)   | -       | -      |
| <i>S. pneumoniae</i> (206)       | 15(7.3)   | 3(8.7)   | 8(12.6)  | 141(81.1) | 39(100)  | -        | -        | -        | -        | -       | -      |
| Viridans group streptococci (18) | 1(5.6)  | -        | 2(16.7)  | 6(50.0)   | 7(88.9)  | 2(100)   | -        | -        | -        | -       | -      |
| <i>Enterococcus</i> spp. (52)    | 2(3.8)  | -        | -        | 1(5.8)    | 13(30.8) | 13(55.8) | 2(59.6)  | -        | 8(75.0)  | 8(90.4) | 5(100) |

a. CoNS = coagulase-negative staphylococci.

**Table 3.** Antimicrobial activity of sitafloxacin in comparison to other quinolones against isolates collected in Latin American medical centers.

| Organism/antimicrobial agent (no. tested) | MIC (µg/ml) |      | % susceptible  | % resistant |
|---|-------------|------|----------------|-------------|
|   | 50%         | 90%  |                |             |
| <i>S. aureus</i>                          |             |      |                |             |
| Oxacillin-susceptible (160)               |             |      |                |             |
| Sitafloxacin                              | 0.015       | 0.03 | - <sup>a</sup> | -           |
| Ciprofloxacin                             | 0.25        | 0.5  | 96.3           | 2.6         |
| Levofloxacin                              | 0.12        | 0.25 | 99.4           | 0.0         |
| Gatifloxacin                              | 0.06        | 0.12 | 100.0          | 0.0         |
| Clindamycin                               | 0.12        | 0.12 | 98.1           | 1.3         |
| Trimethoprim/Sulfamethoxazole             | ≤0.5        | ≤0.5 | 97.5           | 2.5         |
| Vancomycin                                | 1           | 1    | 100.0          | 0.0         |
| <i>S. aureus</i>                          |             |      |                |             |
| Oxacillin-resistant (134)                 |             |      |                |             |
| Sitafloxacin                              | 0.25        | 1    | -              | -           |
| Ciprofloxacin                             | >4          | >4   | 5.2            | 93.3        |
| Levofloxacin                              | 4           | >4   | 9.7            | 30.6        |
| Gatifloxacin                              | 2           | 4    | 71.6           | 6.0         |
| Clindamycin                               | >8          | >8   | 13.4           | 86.6        |
| Trimethoprim/Sulfamethoxazole             | >2          | >2   | 45.1           | 54.9        |
| Vancomycin                                | 1           | 1    | 100.0          | 0.0         |
| CoNS <sup>b</sup>                         |             |      |                |             |
| Oxacillin-susceptible (21)                |             |      |                |             |
| Sitafloxacin                              | 0.015       | 0.03 | -              | -           |
| Ciprofloxacin                             | 0.12        | 0.25 | 95.2           | 4.8         |
| Levofloxacin                              | 0.12        | 0.25 | 95.2           | 4.8         |
| Gatifloxacin                              | 0.12        | 0.12 | 95.2           | 4.8         |
| Clindamycin                               | ≤0.06       | 0.12 | 100.0          | 0.0         |
| Trimethoprim/Sulfamethoxazole             | ≤0.5        | 1    | 95.2           | 4.8         |
| Vancomycin                                | 1           | 2    | 100.0          | 0.0         |
| CoNS <sup>c</sup>                         |             |      |                |             |
| Oxacillin-resistant (116)                 |             |      |                |             |
| Sitafloxacin                              | 0.06        | 0.25 | -              | -           |
| Ciprofloxacin                             | 4           | >4   | 45.7           | 51.7        |
| Levofloxacin                              | 2           | >4   | 58.6           | 23.3        |
| Gatifloxacin                              | 0.5         | 2    | 91.4           | 2.6         |
| Clindamycin                               | 0.5         | >8   | 50.0           | 49.1        |
| Trimethoprim/Sulfamethoxazole             | >2          | >2   | 46.1           | 53.9        |
| Vancomycin                                | 1           | 2    | 100.0          | 0.0         |

## RESULTS

**Table 3.** Continued.

| Organism/antimicrobial agent (no. tested) | MIC (µg/ml) |      | % susceptible | % resistant      |
|---|-------------|------|---------------|------------------|
|   | 50%         | 90%  |               |                  |
| <i>S. pneumoniae</i> (206)                |             |      |               |                  |
| Sitafloxacin                              | 0.03        | 0.06 | -             | -                |
| Ciprofloxacin                             | 1           | 2    | -             | 0.5 <sup>c</sup> |
| Levofloxacin                              | 1           | 1    | 100.0         | 0.0              |
| Gatifloxacin                              | 0.25        | 0.25 | 100.0         | 0.0              |
| Garenoxacin                               | 0.03        | 0.06 | 100.0         | 0.0              |
| Penicillin                                | 0.03        | 2    | 74.8          | 11.7             |
| Ceftriaxone <sup>e</sup>                  | 0.03        | 1    | 99.0          | 0.5              |
| Erythromycin                              | 0.25        | 2    | 87.4          | 11.7             |
| viridans group streptococci (18)          |             |      |               |                  |
| Sitafloxacin                              | 0.03        | 0.12 | -             | -                |
| Ciprofloxacin                             | 2           | 2    | -             | -                |
| Levofloxacin                              | 1           | 2    | 94.4          | 5.6              |
| Gatifloxacin                              | 0.25        | 0.5  | 100.0         | 0.0              |
| Penicillin                                | 0.06        | 2    | 72.2          | 0.0              |
| Ceftriaxone                               | 0.25        | 2    | 88.9          | 0.0              |
| <i>Enterococcus</i> spp. (52)             |             |      |               |                  |
| Sitafloxacin                              | 0.12        | 2    | -             | -                |
| Ciprofloxacin                             | 1           | >4   | 50.0          | 40.4             |
| Levofloxacin                              | 1           | >4   | 59.6          | 40.4             |
| Gatifloxacin                              | 0.5         | >4   | 59.6          | 40.4             |
| Ampicillin                                | ≤2          | 16   | 88.5          | 11.5             |
| Vancomycin                                | 2           | >16  | 84.6          | 11.5             |

a. - = no breakpoint has been established by the NCCLS.  
b. CoNS = coagulase-negative staphylococci.  
c. Percentage of isolates with ciprofloxacin MIC at ≥ 4 µg/ml.

## CONCLUSIONS

- Sitafloxacin was highly active and more potent than currently marketed fluoroquinolones for use against clinical strains of Gram-positive bacteria isolated in selected Latin American medical centers in 2002.

## SELECTED REFERENCES

- Marshall SA, Jones RN. In vitro activity of DU-6859a, a new fluorocyclopropyl quinolone. *Antimicrobial Agents and Chemotherapy* 1993;37:2747-53.
- National Committee for Clinical Laboratory Standards. (2003). *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - sixth edition. Approved document M7-A6*. Wayne, PA:NCCLS.
- National Committee for Clinical Laboratory Standards. (2003). *Performance standards for antimicrobial susceptibility testing, 13th informational supplement M100-S13*. Wayne, PA:NCCLS.
- Schmitz FJ, Fluit AC, Milatovic D, Verhoef J, Heinz HP, Brisse S. In vitro potency of moxifloxacin, clinafloxacin and sitafloxacin against 248 genetically defined clinical isolates of *Staphylococcus aureus*. *Journal of Antimicrobial Chemotherapy* 2000;46:109-13.
- Shetty N, Wilson APF. Sitafloxacin in the treatment of patients with infections caused by vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus*. *Journal of Antimicrobial Chemotherapy* 2000;46: 633-638.