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# Letters to the Editor

## Comparative Activities of Tigecycline and Other Tetracyclines against Nonfermenting Gram-Negative Bacilli, Excluding *Acinetobacter* spp.▽

Tigecycline, a glycylcycline, is a semisynthetic derivative of minocycline with a broad spectrum of activity against aerobic and anaerobic bacteria (2, 12, 16).

In the literature there are several publications concerning tigecycline activity, most of them related to *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* isolates (1, 5, 8, 10, 11, 14); however, its activity against other species of nonfermenting Gram-negative bacilli (NFGNB) has rarely been reported.

Here we determined the activities of tetracycline, doxycycline, minocycline, and tigecycline against 195 clinical isolates of NFGNB (excluding *Acinetobacter* spp.) recovered from clinical materials of patients treated at the Hospital de Clínicas Jose de San Martin, Universidad de Buenos Aires, Argentina,

TABLE 1. *In vitro* susceptibilities of 138 commonly isolated nonfermenting Gram-negative bacillus isolates to tigecycline and other tetracyclines

| Species (no. of isolates) | Drug | MIC (μg/ml) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Range | Breakpoint interpretation[a] | | | $MIC_{50}$ | $MIC_{90}$ |
| | | | S | I | R | | |
| *Achromobacter* spp. (33) | Tetracycline | 2–256 | ≤4 | 8 | ≥16 | 256 | 256 |
| | Doxycycline | 0.5–64 | ≤4 | 8 | ≥16 | 16 | 64 |
| | Minocycline | 0.5–16 | ≤4 | 8 | ≥16 | 2 | 8 |
| | Tigecycline[b] | 0.5–4 | ≤2 | 4 | ≥8 | 2 | 4 |
| *Alcaligenes faecalis* (11) | Tetracycline | 4–32 | ≤4 | 8 | ≥16 | 8 | 16 |
| | Doxycycline | 2–16 | ≤4 | 8 | ≥16 | 2 | 8 |
| | Minocycline | 1–8 | ≤4 | 8 | ≥16 | 2 | 8 |
| | Tigecycline[b] | 1–8 | ≤2 | 4 | ≥8 | 2 | 4 |
| *Burkholderia cepacia* complex (21) | Tetracycline | 0.03–256 | ≤4 | 8 | ≥16 | 16 | 64 |
| | Doxycycline | 0.06–16 | ≤4 | 8 | ≥16 | 4 | 4 |
| | Minocycline[c] | 0.03–4 | ≤4 | 8 | ≥16 | 1 | 2 |
| | Tigecycline[b] | 0.03–2 | ≤2 | 4 | ≥8 | 0.5 | 2 |
| *Chryseobacterium gleum-indologenes* (11) | Tetracycline | 0.06–32 | ≤4 | 8 | ≥16 | 8 | 32 |
| | Doxycycline | 0.125–16 | ≤4 | 8 | ≥16 | 1 | 8 |
| | Minocycline | 0.03–2 | ≤4 | 8 | ≥16 | 0.25 | 1 |
| | Tigecycline[b] | 0.03–4 | ≤2 | 4 | ≥8 | 1 | 4 |
| *Elizabethkingia meningoseptica* (15) | Tetracycline | 2–128 | ≤4 | 8 | ≥16 | 32 | 64 |
| | Doxycycline | 1–32 | ≤4 | 8 | ≥16 | 2 | 4 |
| | Minocycline | 0.06–2 | ≤4 | 8 | ≥16 | 0.25 | 0.5 |
| | Tigecycline[b] | 0.25–8 | ≤2 | 4 | ≥8 | 2 | 8 |
| *Stenotrophomonas maltophilia* (26) | Tetracycline | 0.5–64 | ≤4 | 8 | ≥16 | 8 | 16 |
| | Doxycycline | 1–4 | ≤4 | 8 | ≥16 | 2 | 2 |
| | Minocycline[d] | 0.25–2 | ≤4 | 8 | ≥16 | 0.25 | 0.5 |
| | Tigecycline[b] | 0.125–8 | ≤2 | 4 | ≥8 | 0.5 | 2 |
| *Pseudomonas putida* (11) | Tetracycline | 0.125–256 | ≤4 | 8 | ≥16 | 2 | 16 |
| | Doxycycline | 0.06–128 | ≤4 | 8 | ≥16 | 4 | 32 |
| | Minocycline | 0.06–32 | ≤4 | 8 | ≥16 | 2 | 16 |
| | Tigecycline[b] | 0.25–16 | ≤2 | 4 | ≥8 | 2 | 8 |
| *Pseudomonas stutzeri* group (10) | Tetracycline | 0.125–8 | ≤4 | 8 | ≥16 | 0.5 | 4 |
| | Doxycycline | 0.25–8 | ≤4 | 8 | ≥16 | 2 | 8 |
| | Minocycline | 0.5–8 | ≤4 | 8 | ≥16 | 1 | 4 |
| | Tigecycline[b] | 0.06–4 | ≤2 | 4 | ≥8 | 0.25 | 2 |

[a] S, sensitive; I, intermediate; R, resistant. CLSI categories for other non-*Enterobacteriaceae* for tetracycline, doxycycline, and minocycline were used (susceptibility at 4 μg/ml, intermediacy at 8 μg/ml, and resistance at 16 μg/ml).

[b] Breakpoint recommended by the U.S. Food and Drug Administration when testing *Enterobacteriaceae* for tigecycline (susceptibility at 2 μg/ml, intermediacy at 4 μg/ml, and resistance at 8 μg/ml).

[c] *Burkholderia cepacia* CLSI breakpoint recommended for minocycline.

[d] *Stenotrophomonas maltophilia* CLSI breakpoint recommended for minocycline.

TABLE 2. *In vitro* susceptibilities of 57 uncommonly isolated nonfermenting Gram-negative bacillus isolates to tigecycline and other tetracyclines

| Species | No. of isolates | MIC range (μg/ml) | | | |
|---|---|---|---|---|---|
| | | Tetracycline | Doxycycline | Minocycline | Tigecycline |
| *Rhizobium radiobacter* | 5 | 0.25–4 | 0.25–0.5 | 0.06–0.5 | 0.5–0.5 |
| *Ochrobactrum anthropi* | 8 | 0.5–16 | 0.06–8 | ≤0.03–2 | 0.25–2 |
| *Burkholderia gladioli* | 2 | 4–64 | 2–4 | 1–4 | 1–2 |
| *Bordetella bronchiseptica* | 3 | 0.5–0.5 | 0.25–0.25 | 0.25–0.25 | 0.25–0.25 |
| *Bordetella hinzii* | 3 | 0.5–4 | 0.25–1 | 0.25–0.5 | 0.25–0.5 |
| *Delftia acidovorans* | 3 | 0.5–2 | 0.125–0.25 | 0.06–0.25 | 0.125–0.5 |
| *Pseudomonas oryzihabitans* | 6 | 0.5–4 | 0.25–4 | 0.25–4 | ≤0.03–4 |
| *Pseudomonas pseudoalcaligenes* | 3 | 0.5–4 | 2–4 | 2–4 | 0.25–1 |
| *Shewanella algae* | 5 | 0.25–1 | 0.25–1 | 0.06–0.25 | 0.125–0.5 |
| *Sphingomonas paucimobilis* | 7 | 0.25–4 | 0.125–1 | <0.03–0.06 | 0.25–1 |
| *Sphingobacterium multivorum* | 2 | 2–4 | 1–2 | 0.06–0.25 | 0.25–0.25 |
| *Myroides* spp. | 5 | 2–128 | 0.5–16 | 0.06–0.5 | 0.5–4 |
| *Pandoraea* spp.[a] | 4 | 4–128 | 1–64 | 1–16 | 2–32 |
| *Inquilinus limosus* | 1 | 128 | 16 | 2 | 0.5 |

[a] *P. pnomenusa* ($n = 1$), *P. apista* ($n = 1$), *P. pulmonicola* ($n = 1$), and *P. sputorum* ($n = 1$).

during the 1995–2009 period. Only one isolate per patient was included in the study.

All the isolates were identified using standard biochemical tests (15) and API 20NE (bioMérieux, Marcy l'Etoile, France). PCR amplification of the 16S rRNA was performed in order to identify *Burkholderia cepacia* complex, *Burkholderia gladioli*, *Pandoraea* spp., *Inquilinus limosus*, and *Bordetella hinzii* using the primers described by Weisburg et al. (17).

Susceptibility was determined by agar dilution (Mueller-Hinton agar was from Difco, BBL) according to the Clinical and Laboratory Standards Institute (CLSI) recommendations (3). MIC determination for tigecycline and the other tetracyclines was performed using freshly prepared agar with the antibiotic incorporated into the medium on the day of use and inoculated within a few hours.

Control strains for the agar dilution test included *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Staphylococcus aureus* ATCC 29213, and *Enterococcus faecalis* ATCC 29212.

Drug powders were obtained commercially or provided by their respective manufacturers.

The MIC breakpoints for tetracycline, doxycycline, and minocycline were interpreted using CLSI categories (4) for other non-*Enterobacteriaceae*: susceptibility at 4 μg/ml, intermediacy at 8 μg/ml, and resistance at 16 μg/ml. In addition, those recommended by CLSI for *Burkholderia cepacia* and for *Stenotrophomonas maltophilia* for minocycline (susceptibility at 4 μg/ml, intermediacy at 8 μg/ml, and resistance at 16 μg/ml) and those recommended by the U.S. Food and Drug Administration (FDA) when testing *Enterobacteriaceae* (susceptibility at 2 μg/ml, intermediacy at 4 μg/ml, and resistance at 8 μg/ml) for tigecycline were used.

$MIC_{50}$ and $MIC_{90}$ values, together with the MIC ranges of NFGNB isolates, are shown in Tables 1 and 2.

Tigecycline was active against most species tested. Also, it was more active than minocycline against *Pseudomonas pseudoalcaligenes*, the *Pseudomonas stutzeri* group, and *Pseudomonas oryzihabitans*. However, its activity was lower than that of minocycline against members of the *Flavobacteriaceae* (*Elizabethkingia meningoseptica* and *Chryseobacterium gleum-indologenes*) and *Myroideaceae* families and against *S. maltophilia*. The observed behavior against *S. maltophilia* has also been reported by other authors (1, 11, 13). In addition, the $MIC_{90}$ for tigecycline ($MIC_{90}$, 2 μg/ml) was slightly lower than that previously reported by other authors (1, 6, 7, 13) and in agreement with those reported by Milatovic et al. (11).

Concerning the activity of tigecycline against *E. meningoseptica* isolates, our results ($MIC_{90}$, 8 μg/ml) differ from those reported by Lin et al., who obtained 88.5% sensitivity against isolates tested ($MIC_{90}$, 3 μg/ml) (9). However, this discrepancy could be attributed to the different assessment methods of antimicrobial susceptibility used in the two cases.

None of the tetracyclines tested were active against *Pseudomonas putida*, and all had weak activity against *Achromobacter* spp. and *Alcaligenes faecalis*.

The lowest MIC values for tigecycline were observed against *Shewanella algae*, *Sphingomonas paucimobilis*, *Delftia acidovorans*, *Rhizobium radiobacter*, *Pseudomonas oryzihabitans*, and *Bordetella* species.

Regarding *Burkholderia cepacia* complex isolates, minocycline and tigecycline had comparable activities ($MIC_{90}$, 2 μg/ml), and in contrast to the report by Milatovic et al. (11), 100% of isolates assayed in the present study were susceptible to both antibiotics; however, our work, like the others, does not report which *Burkholderia cepacia* complex genomovars were included in both studies.

Our results indicate that tigecycline could be a therapeutic option for the treatment of nonfermenting Gram-negative bacillus infections in view of the multidrug resistance observed in several species.

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## REFERENCES

1. **Betriu, C., I. Rodríguez-Avial, B. A. Sánchez, M. Gómez, and J. J. Picazo.** 2002. Comparative in vitro activities of tigecycline (GAR-936) and other antimicrobial agents against *Stenotrophomonas maltophilia*. J. Antimicrob. Chemother. **50:**758–759.
2. **Bradford, P. A., D. T. Weaver-Sands, and P. J. Petersen.** 2005. In vitro activity of tigecycline against isolates from patients enrolled in phase 3 clinical trials of treatment for complicated skin and skin-structure infections and complicated intra-abdominal infections. Clin. Infect. Dis. **41**(Suppl. 5)**:** S315–S332.
3. **Clinical and Laboratory Standards Institute.** 2008. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 7th ed. Approved standard M7-A7. Clinical and Laboratory Standards Institute, Wayne, PA.
4. **Clinical and Laboratory Standards Institute.** 2008. Performance standards for antimicrobial susceptibility testing; M100-S18, 18th informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.

5. **Farrell, D. J., H. S. Sader, and R. N. Jones.** 2010. Antimicrobial susceptibilities of a worldwide collection of *Stenotrophomonas maltophilia* isolates tested against tigecycline and agents commonly used for *S. maltophilia* infections. Antimicrob. Agents Chemother. **54:**2735–2737.
6. **Gales, A. C., and R. N. Jones.** 2000. Antimicrobial activity and spectrum of the new glycylcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates. Diagn. Microbiol. Infect. Dis. **36:**19–36.
7. **Gómez-Garcés, J. L., B. Aracil, and Y. Gil.** 2009. Comparison between agar dilution and three other methods for determining the susceptibility of 228 clinical isolates of non-fermenting gram-negative rods. Enferm. Infecc. Microbiol. Clin. **27:**331–337.
8. **Insa, R., E. Cercenado, M. J. Goyanes, A. Morente, and E. Bouza.** 2007. In vitro activity of tigecycline against clinical isolates of *Acinetobacter baumannii* and *Stenotrophomonas maltophilia*. J. Antimicrob. Chemother. **59:**583–585.
9. **Lin, Y. T., et al.** 2009. Tigecycline and colistin susceptibility of *Chryseobacterium meningosepticum* isolated from blood in Taiwan. Int. J. Antimicrob. Agents **34:**100–101.
10. **Mendes, R. E., D. J. Farrell, H. S. Sader, and R. N. Jones.** 2010. Comprehensive assessment of tigecycline activity tested against a worldwide collection of *Acinetobacter* spp. (2005–2009). Diagn. Microbiol. Infect. Dis. **68:** 307–311.
11. **Milatovic, D., F. J. Schmitz, J. Verhoef, and A. C. Fluit.** 2003. Activities of the glycylcycline tigecycline (GAR-936) against 1,924 recent European clinical bacterial isolates. Antimicrob. Agents Chemother. **47:**400–404.
12. **Noskin, G. A.** 2005. Tigecycline: a new glycylcycline for treatment of serious infections. Clin. Infect. Dis. **41**(Suppl. 5)**:**S303–S314.
13. **Petersen, P. J., N. V. Jacobus, W. J. Weiss, P. E. Sum, and R. T. Testa.** 1999. In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936). Antimicrob. Agents Chemother. **43:**738–744.
14. **Sader, H. S., D. J. Farrell, and R. N. Jones.** 2011. Tigecycline activity tested against multidrug-resistant *Enterobacteriaceae* and *Acinetobacter* spp. isolated in US medical centers (2005–2009). Diagn. Microbiol. Infect. Dis. **69:**223–227.
15. **Schreckenberger, P., M. Daneshvar, and D. Hollis.** 2007. *Acinetobacter*, *Achromobacter*, *Chryseobacterium*, *Moraxella*, and other non-fermentative Gram-negative rods, p. 770–802. *In* P. R. Murray, E. J. Baron, J. H. Jorgensen, M. L. Landry, and M. A Pfaller (ed.), Manual of clinical microbiology, 9th ed. ASM Press, Washington, DC.
16. **Stein, G. E., and W. A. Craig.** 2006. Tigecycline: a critical analysis. Clin. Infect. Dis. **43:**518–524.
17. **Weisburg, W. G., S. M. Barns, D. A. Pelletier, and L. D. Lane.** 1991. 16S ribosomal DNA amplification for phylogenetic study. J. Bacteriol. **173:** 697–703.

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