

Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program - In Vitro Antibacterial Activity of Tigecycline at Flinders Medical Centre, South Australia

#1.10

D. Gordon¹, B. Johnson², S. Bouchillon², H.Pruul¹, M. Dowzicky³

¹Flinders Medical Centre, South Australia, Australia
²International Health Management Associates, Schaumburg, IL, USA
³Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL 60173
Tel: (847) 303-5003
Fax: (847) 303-5601
www.ihmainc.com

REVISED ABSTRACT

Background: Tigecycline, the first of a new antimicrobial class of glycyclines in clinical trials, has been shown to have potent activity against most species of Gram-positive and -negative bacteria. The T.E.S.T. program determined the in vitro activity of tigecycline compared to amikacin, ampicillin, amoxicillin/clavulanic acid, imipenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline, piperacillin/tazobactam, linezolid, penicillin and vancomycin against selected clinical isolates collected from one investigational site, Flinders Medical Centre in South Australia. **Methods:** Minimum Inhibitory Concentration (MICs) of 187 clinical bacterial isolates collected during 2005 were determined by broth microdilution and interpreted according to CLSI guidelines. **Results:** The broad-spectrum antimicrobials levofloxacin, cefepime, amikacin, and imipenem were highly active against Gram-negative strains in this study and demonstrated susceptible percentages rates of 100%. Tigecycline's activity was comparable to imipenem and cefepime presenting MIC₉₀ values ranging from 0.06 to 2 mcg/mL against all Gram-negative strains (excluding *Pseudomonas*). Tigecycline MIC₉₀ values ranged from 0.06 to 1 mcg/mL against all Gram-positive strains and were equivalent to linezolid and vancomycin against *S. pneumoniae* and 4- and 32-fold lower than those for linezolid and vancomycin against staphylococci and enterococci. Tigecycline was also successful in inhibiting 100% of *S. aureus* regardless of methicillin phenotypes at a MIC of ≤ 0.5 mcg/mL. Tigecycline inhibited all *H. influenzae* at ≤ 0.25 mcg/mL without regard to beta-lactamase production. **Conclusion:** Tigecycline's activity was comparable to the activities of broad spectrum antimicrobials and highly effective most strains of Gram-negative and Gram-positive bacteria. Tigecycline's activity was comparable to imipenem, linezolid and vancomycin which are often considered as last therapeutic option for the treatment of serious nosocomial infections caused by this class of organisms. Tigecycline, as other tetracyclines, had limited activity against *P. aeruginosa*. These data present strong in vitro antibiogram activity for tigecycline in one teaching medical centre in South Australia.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, its anti-bacterial activity is significant and has shown some bactericidal activity against key targeted pathogens [1,2]. Tigecycline was developed to provide activity against tetracycline and multi-drug-resistant Gram-positive pathogens and has demonstrated significant broad-spectrum activity against aerobic and anaerobic Gram-positive and Gram-negative microorganisms [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency observed at less than 10⁻⁹ [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. Tigecycline has shown to be a highly effective against multi-resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum β -lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC₉₀ values of ≤ 0.5 mcg/mL against methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity against animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4, 5] with diverse genotypes van-A, -B and -C [6].

This study was designed to communicate one laboratory's in vitro experience with activity of tigecycline in a limited number of clinical isolates collected from Flinders Medical Centre in South Australia.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted.
- Clinical isolates (n=187) were collected tested between January 2005 - December 2005 from a single study center from South Australia.
- Custom broth microdilution panels were supplied by MicroScan (Dade MicroScan, Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/mL): amoxicillin/clavulanic acid (0.03-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-32); ceftriaxone (0.03-64); cefepime (0.5-32); ampicillin (0.06-32); amikacin (0.5-64); minocycline (0.25-16); ceftazidime (8-32); tigecycline (0.008-16); imipenem (0.06-16); linezolid (0.5-8); penicillin (0.06-8); and vancomycin (0.12-32).
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [12].
- MIC interpretive criteria for tigecycline followed published guidelines established by the FDA where applicable [13].
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Quality control of broth microdilution panels followed manufacture's and NCCLS guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853.
- The collection and transportation of organisms and the confirmation of identification, as well as, construction and management of a centralized database were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).

REFERENCES

- Sum, P.E. and P. Petersen. Synthesis and structure-activity relationship of novel glycycline derivatives leading to the discovery of GAR-936. *Bioorg Med Chem Lett*. 1999; 9(10): p. 1459-62.
- Abstrak, D., M. Macleod, and K. Bush. Novel antibacterial agents for the treatment of serious Gram-positive infections. *Expert Opin Investig Drugs*. 2003; 12(3): p. 379-99.
- Betzu, C., et al. In vitro activities of tigecycline (GAR-936) against recently isolated clinical bacteria in Spain. *Antimicrob Agents Chemother*. 2002; 46(2): p. 892-4.
- Gates, A.C. and R.N. Jones. Antimicrobial activity and spectrum of the new glycycline, GAR-936 tested against 1,203 recent clinical bacterial isolates. *Diagn Microbiol Infect Dis*. 2003; 36(1): p. 19-26.
- Henwood, C.J., et al. Antibiotic resistance among clinical isolates of *Acinetobacter* in the UK, and in vitro evaluation of tigecycline (GAR-936). *J Antimicrob Chemother*. 2002; 49(3): p. 478-87.
- Chopis, I. New developments in tetracycline antibiotics: glycyclines and tetracycline efflux pump inhibitors. *Drug Resist Update*. 2002; 5(3-4): p. 119-25.
- Projan, S.J. Preclinical pharmacology of GAR-936, a novel glycycline antibacterial agent. *Pharmacotherapy*. 2000; 20(9 Pt 2): p. 2195-2235; discussion 2245-2255.
- Biedenbach, D.J., M.L. Beach, and R.N. Jones. In vitro antimicrobial activity of GAR-936 tested against antibiotic-resistant gram-positive blood stream infection isolates and strains producing extended-spectrum beta-lactamases. *Diagn Microbiol Infect Dis*. 2001; 45(4): p. 173-7.
- Patel, R., et al. In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis*. 2003; 36(3): p. 177-9.
- Petersen, P.J., et al. In vitro and in vivo antibacterial activities of a novel glycycline, the 91-butylglycylamido derivative of minocycline (GAR-936). *Antimicrob Agents Chemother*. 1999; 43(4): p. 178-84.
- Petersen, P.J., et al. In vitro and in vivo activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate *Staphylococcus aureus* and other resistant gram-positive pathogens. *Antimicrob Agents Chemother*. 2002; 46(8): p. 2595-601.
- National Committee for Clinical Laboratory Standards (NCCLS). Performance Standards for Antimicrobial Susceptibility Testing. Fourteenth Informational Supplement. CLSI document M100-S15. Wayne, PA, 2005.
- Tigecycline. 2005. Tigecycline FDA package insert.

ACKNOWLEDGEMENTS

This study was supported by a grant from Wyeth Pharmaceuticals.

RESULTS

The results are listed in the following Tables.

Table 1. Flinders Medical Centre Antibiogram for Tigecycline and 13 Comparators with Percent Susceptible and MIC₉₀ (mcg/mL) against 187 strains of selected Gram-negative and Gram-positive Pathogens

Organism (n)	Percent Susceptible (%) (MIC ₉₀)													
	Tigecycline	Amikacin	AmoxClav	Ampicillin	Cefepime	Ceftazidime	Ceftriaxone	Imipenem	Levofloxacin	Linezolid	Minocycline	Penicillin	PipTazo	Vancomycin
<i>Acinetobacter baumannii</i> (5)	* (1)	100 (8)	* (>32)	* (>32)	60 (32)	80 (>32)	20 (>64)	100 (1)	80 (8)	-	100 (4)	-	100 (16)	-
<i>Acinetobacter lwofii</i> (1)	* (0.06)	100 (1)	* (4)	* (4)	100 (1)	100 (≤ 8)	100 (4)	100 (0.25)	100 (0.12)	-	100 (≤ 0.5)	-	100 (≤ 0.06)	-
<i>Enterobacter aerogenes</i> (6)	100 (0.5)	100 (4)	* (>32)	* (>32)	100 (1)	16.7 (32)	100 (8)	100 (1)	100 (0.06)	-	100 (4)	-	66.7 (64)	-
<i>Enterobacter cloacae</i> (19)	89.5 (8)	100 (4)	* (>32)	* (>32)	100 (4)	36.8 (>32)	42.1 (>64)	100 (1)	100 (0.25)	-	84.2 (>16)	-	42.1 (64)	-
<i>Enterobacteriaceae</i> (84)	96.4 (1)	100 (4)	50.0 (>32)	14.3 (>32)	100 (2)	76.6 (32)	85.7 (32)	100 (1)	100 (0.25)	-	89.3 (4)	-	78.6 (64)	-
<i>Enterococcus casseliflavus</i> (1)	* (0.12)	-	* (0.5)	100 (0.5)	-	-	* (16)	* (0.5)	100 (2)	100 (2)	* (8)	100 (0.5)	* (4)	100 (4)
<i>Enterococcus faecalis</i> (12)	100 (0.12)	-	* (1)	100 (1)	-	-	* (>64)	* (1)	66.7 (32)	100 (2)	8.3 (>8)	100 (4)	* (4)	100 (2)
<i>Enterococcus faecium</i> (4)	* (0.06)	-	* (>8)	* (>16)	-	-	* (>64)	* (>16)	* (>32)	100 (2)	100 (4)	* (>8)	* (>16)	100 (2)
<i>Escherichia coli</i> (25)	100 (0.25)	100 (8)	92 (8)	48 (>32)	100 (≤ 0.5)	96 (≤ 8)	100 (0.12)	100 (0.5)	100 (0.12)	-	92 (4)	-	100 (2)	-
<i>Haemophilus influenzae</i> (14)	* (0.25)	* (16)	100 (2)	78.6 (2)	100 (≤ 0.5)	* (≤ 8)	100 (≤ 0.06)	100 (1)	100 (0.12)	-	* (1)	-	100 (≤ 0.06)	-
<i>Klebsiella oxytoca</i> (8)	100 (1)	100 (4)	50 (32)	* (>32)	100 (8)	100 (≤ 8)	87.5 (16)	100 (1)	100 (2)	-	100 (4)	-	50 (>128)	-
<i>Klebsiella pneumoniae</i> (16)	93.8 (1)	100 (2)	93.8 (4)	* (>32)	100 (≤ 0.5)	100 (≤ 8)	100 (0.5)	100 (0.5)	100 (0.25)	-	93.8 (4)	-	93.8 (8)	-
<i>Pseudomonas aeruginosa</i> (20)	* (16)	90 (8)	* (>32)	* (>32)	60 (32)	85 (32)	5 (>64)	90 (4)	55 (>8)	-	* (>16)	-	85 (128)	-
<i>Serratia marcescens</i> (10)	100 (2)	100 (4)	* (>32)	* (>32)	100 (1)	100 (≤ 8)	100 (1)	100 (2)	100 (0.25)	-	70 (8)	-	100 (4)	-
<i>Staphylococcus aureus</i> , MRSA (8)	100 (0.5)	-	25 (>8)	* (>16)	-	-	* (>64)	50 (>16)	25 (8)	100 (2)	75 (8)	* (>8)	12.5 (>16)	100 (2)
<i>Staphylococcus aureus</i> , MSSA (17)	100 (0.12)	-	100 (1)	11.8 (>16)	-	-	94.1 (4)	100 (0.25)	100 (1)	100 (2)	100 (≤ 0.25)	11.8 (>8)	100 (4)	100 (1)
<i>Streptococcus agalactiae</i> (8)	100 (0.06)	-	* (0.5)	100 (0.25)	-	-	100 (0.5)	* (0.25)	100 (0.5)	100 (1)	* (>8)	100 (0.12)	* (0.5)	100 (0.5)
<i>Streptococcus pneumoniae</i> (13)	* (1)	-	92.3 (1)	* (1)	-	-	100 (1)	92.3 (<0.12)	100 (1)	100 (1)	* (1)	69.2 (1)	* (2)	100 (0.5)

* Breakpoint undefined for this species/drug combination.
- not tested

Table 2. Flinders Medical Centre Frequency Distribution (n) and Cumulative Percents Inhibited (%) of Tigecycline against 187 strains of selected Gram-negative and Gram-positive Pathogens

Organism (n)	MIC (mcg/mL)											
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16
<i>Acinetobacter baumannii</i> (5)				2		1	2					
<i>Acinetobacter lwofii</i> (1)			1									
<i>Enterobacter aerogenes</i> (6)			100									
<i>Enterobacter cloacae</i> (19)					33.3	100						
<i>Enterobacteriaceae</i> (84)					5.3	73.7	84.2	89.5	89.5	100		
<i>Enterococcus casseliflavus</i> (1)				20	19	26	13	3	1	2		
<i>Enterococcus faecalis</i> (12)				23.8	46.4	77.4	92.9	96.5	97.7	100		
<i>Enterococcus faecium</i> (4)												
<i>Escherichia coli</i> (25)												
<i>Haemophilus influenzae</i> (14)												
<i>Klebsiella oxytoca</i> (8)												
<i>Klebsiella pneumoniae</i> (16)												
<i>Pseudomonas aeruginosa</i> (20)												
<i>Serratia marcescens</i> (10)												
<i>Staphylococcus aureus</i> , MRSA (8)												
<i>Staphylococcus aureus</i> , MSSA (17)												
<i>Streptococcus agalactiae</i> (8)												
<i>Streptococcus pneumoniae</i> (13)												

CONCLUSIONS

- Tigecycline inhibited 96.4% of all *Enterobacteriaceae* tested in vitro at a MIC₉₀ of 1 mcg/mL. Tigecycline's MIC₉₀ of 1 mcg/mL was equivalent to imipenem and 8 to 64 fold better than the beta-lactams, beta-lactam/beta-lactamase inhibitor combinations. Only levofloxacin had a lower MIC₉₀ at 0.25 mcg/mL against all *Enterobacteriaceae* tested.
- Tigecycline showed potent activity against *A. baumannii* with the lowest MIC₉₀ value of 1 mcg/mL.
- Tigecycline's limited activity against *P. aeruginosa* is similar to other tetracyclines and their analog derivatives.
- Tigecycline showed potent inhibitory activity against *S. aureus* regardless of methicillin-resistant phenotype. Tigecycline inhibited the growth of all *S. aureus* at a MIC of 0.5 mcg/mL.
- Tigecycline had the lowest MIC₉₀ value of all comparative agents against both *E. faecium* and *E. faecalis* at 0.06 and 0.12 mcg/mL, respectively. Tigecycline inhibited 100% of enterococci at MICs equal to or below 0.12 mcg/mL.
- Tigecycline inhibited all *H. influenzae* at an MIC equal to or below 0.25 mcg/mL.
- Tigecycline inhibited all *S. pneumoniae* at or below 1 mcg/mL without regard to penicillin susceptibility phenotypes.
- The in vitro activity of tigecycline in this study suggests that tigecycline is an effective agent with excellent antimicrobial in this single clinical laboratory against common Gram-negative and Gram-positive nosocomial and community acquired pathogens.