

The In-Vitro Antibacterial Activity of Tigecycline from an Asia/Pacific Rim Population - The T.E.S.T. Program 2006

#P1.11

S. Bouchillon¹, M. Hackel¹, J. Johnson¹, D. Hoban¹, B. Johnson¹, M. Dowzicky²

¹International Health Management Associates, Schaumburg, IL, USA
²Wyeth 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 (TIG), a new glycylycine, has been shown to have potent broad spectrum activity against most commonly encountered species responsible for community and hospital acquired infections. The T.E.S.T. program determined the in vitro activity of TIG and 10 comparators against respective gram positive/negative species. Isolates were collected from 15 study sites across 7 countries of Asia and Pacific Rim from 2004 through 2006. **Methods:** Over 2,376 clinically significant isolates were identified to the species level at participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Selected pathogens tested against tigecycline are shown in the table below:

Organism (#)	Tigecycline		% inhibited at				%S*
	50%	90%	≤0.5	1	2	4	
<i>Enterobacteriaceae</i> (1,083)	0.5	1	79	92.7	98.1	99.4	98.1
ESBLs (104)	0.5	1	78.8	91.3	98.1	100	98.1
<i>A. baumannii</i> (156)	0.25	1	78.8	94.9	96.2	99.4	na
<i>P. aeruginosa</i> (294)	8	>16	2	4.1	5.4	19.7	na
<i>H. influenzae</i> (149)	0.12	0.25	100	-	-	-	na
<i>S. pneumoniae</i> (142)	0.25	0.5	100	-	-	-	na
<i>E. faecalis/faecium</i> (188)	0.12	0.25	100	-	-	-	100
<i>S. aureus</i> (286)	0.12	0.25	100	-	-	-	100
<i>S. agalactiae</i> (78)	0.03	0.12	100	-	-	-	100

*Breakpoints are defined by the FDA (Tygacil[®] package insert, 2005).
†FDA susceptible breakpoint of 0.25 mcg/mL for vancomycin-susceptible *E. faecalis* has been expanded to include all enterococci for comparative purposes only.
na = Breakpoints not yet established for this species.

Conclusion: TIG has been described an expanded broad spectrum antimicrobial because of its consistent activity against *Enterobacteriaceae* including ESBL producing phenotypes, *S. aureus*, including methicillin-resistant strains, *S. pneumoniae*, including penicillin-resistant strains, and both vancomycin-sensitive and vancomycin-resistant enterococci spp. TIG wide spectrum of activity promises to provide enhanced antimicrobial coverage of serious nosocomial/community pathogens.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylycines. 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 beta-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 better define the in vitro activity of tigecycline in a limited number of clinical isolates collected from study centers across Asia and Pacific Rim regions.

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. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Clinical isolates (n=2,376) were collected tested between January 2004 - December 2006 from 15 study centers across Asia and the Pacific Rim countries.
- 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 for all drugs except tigecycline followed published guidelines established by the CLSI where applicable [12]. MIC interpretive criteria for tigecycline followed criteria established by the Federal Drug Administration (FDA, United States, 2005) where applicable [13].
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Klebsiella pneumoniae* ATCC 700603 (positive ESBL control); *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

1. Sum, P.E. and P. Petersen. *Synthesis and structure-activity relationship of novel glycylycine derivatives leading to the discovery of GAR-936*. Bioorg Med Chem Lett, 1999, 9(10): p. 1459-62.
2. Abratt, 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.
3. Berru, C., et al., *In vitro activities of tigecycline (GAR-936) against recently isolated clinical bacteria in Spain*. Antimicrob Agents Chemother, 2002, 46(3): p. 892-5.
4. Gales, A.C. and R.N. Jones. *Antimicrobial activity and spectrum of the new glycylycine, GAR-936 tested against 1,203 recent clinical bacterial isolates*. Diagn Microbiol Infect Dis, 2000, 36(1): p. 19-36.
5. 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. 479-87.
6. Chopra, I., *New developments in tetracycline antibiotics: glycylycines and tetracycline efflux pump inhibitors*. Drug Resist Update, 2002, 5(3-4): p. 119-25.
7. Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycylycine antibacterial agent*. Pharmacotherapy, 2000, 20(9 Pt 2): p. 219S-223S; discussion 224S-228S.
8. 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, 40(4): p. 173-7.
9. 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, 2000, 38(3): p. 177-9.
10. Petersen, P.J., et al., *In vitro and in vivo antibacterial activities of a novel glycylycine, the 9-butylglycylamido derivative of minocycline (GAR-936)*. Antimicrob Agents Chemother, 1999, 43(4): p. 738-44.
11. 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.
12. Clinical Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*. 16th Informational Supplement. CLSI document M100-S16. Wayne, PA, 2006.
13. Tygacil[®], 2005. Tigecycline FDA package insert.

ACKNOWLEDGEMENTS

This study was supported by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge contributions to the T.E.S.T. program from the following participating institutions: P.D. Hinduja National Hospital, India; Research Institute for Tropical Medicine, Philippines and Peking Union Medical College Hospital, China; Singapore General Hospital, Singapore; Aga Khan University & Hospital, Pakistan; Flinders Medical Centre, Philippines.

RESULTS

Results are published in the following tables.

Table 1. In vitro Activity of Tigecycline and Comparative Agents against *Enterobacteriaceae*.

Organism	Drug	%Sus*	%Int	%Res	MIC (mcg/mL)			
					MIC ₅₀	MIC ₉₀	MIC ₉₉	
All <i>Enterobacteriaceae</i> (n=1,083)	Tigecycline	98.1	1.4	0.6	0.5	1		
	Amikacin	95.5	0.3	4.2	2	8		
	Amox-Clav	41.5	12.9	45.6	16	>32		
	Ampicillin	9.2	4	86.8	>32	>32		
	Cefepime	87	3.3	9.7	≤0.5	16		
	Ceftazidime	77.8	4.7	17.5	≤8	>32		
	Ceftriaxone	73.9	6.5	19.7	0.12	>64		
	Imipenem	99.8	0.2	0	0.25	1		
	Levofloxacin	79.4	3.1	17.5	0.06	>8		
	Minocycline	80.7	10	9.3	2	8		
	Pip-Tazo	88.6	6.6	4.8	2	32		
	ESBL producers:	Tigecycline	98.1	1.9	0	0.5	1	
	<i>E. coli</i> , <i>Klebsiella</i> spp. (n=104)	Amikacin	88.5	0	11.5	4	>64	
		Amox-Clav	26.9	51	22.1	16	32	
Ampicillin		1	0	99	>32	>32		
Cefepime		51	11.5	37.5	8	>32		
Ceftazidime		42.3	16.3	41.3	16	>32		
Ceftriaxone		18.3	10.6	71.2	>64	>64		
Imipenem		100	0	0	0.25	0.5		
Levofloxacin		45.2	6.7	48.1	4	>8		
Minocycline		67.3	11.5	21.2	4	16		
Pip-Tazo		86.5	10.6	2.9	4	32		
<i>Enterobacter aerogenes</i> (n=81)		Tigecycline	93.8	3.7	2.5	0.5	1	
		Amikacin	96.3	1.2	2.5	2	4	
		Amox/Clav	2.5	0	97.5	>32	>32	
		Ampicillin	0	0	100	>32	>32	
	Cefepime	93.8	1.2	4.9	≤0.5	2		
	Ceftazidime	64.2	8.6	27.2	≤8	>32		
	Ceftriaxone	85.2	7.4	7.4	0.25	16		
	Imipenem	100	0	0	0.5	1		
	Levofloxacin	93.8	3.7	2.5	0.06	0.25		
	Minocycline	90.1	3.7	6.2	2	4		
	Pip-Tazo	84	13.6	2.5	2	32		
	<i>Enterobacter cloacae</i> (n=183)	Tigecycline	98.4	0.5	1.1	0.5	2	
		Amikacin	95.2	0	4.8	2	4	
		Amox/Clav	2.6	0.5	96.8	>32	>32	
Ampicillin		0	3.7	96.3	>32	>32		
Cefepime		84.7	2.6	12.7	≤0.5	>32		
Ceftazidime		61.9	5.3	32.8	≤8	>32		
Ceftriaxone		58.7	13.8	27.5	1	>64		
Imipenem		100	0	0	0.5	1		
Levofloxacin		87.8	4.2	7.9	0.06	4		
Minocycline		78.8	10.1	11.1	2	16		
Pip-Tazo		76.7	15.9	7.4	2	64		
<i>Escherichia coli</i> (n=341)		Tigecycline	100	0	0	0.12	0.25	
		Amikacin	97.4	0.3	2.3	2	8	
		Amox/Clav	65.4	23.2	11.4	8	32	
	Ampicillin	29.3	0	70.7	>32	>32		
	Cefepime	86.5	3.2	10.3	≤0.5	32		
	Ceftazidime	88.6	4.4	7	≤8	16		
	Ceftriaxone	77.1	3.2	19.6	≤0.06	>64		
	Imipenem	100	0	0	0.25	0.5		
	Levofloxacin	61.6	3.8	34.6	0.25	>8		
	Minocycline	74.2	16.1	9.7	2	8		
	Pip-Tazo	95.9	2.1	2.1	1	8		
	<i>Klebsiella pneumoniae</i> (n=277)	Tigecycline	97.1	2.9	0	0.5	1	
		Amikacin	92.4	0	7.6	2	8	
		Amox/Clav	62.5	17.3	20.2	4	>32	
Ampicillin		0	8.7	91.3	>32	>32		
Cefepime		81.6	6.9	11.6	≤0.5	32		
Ceftazidime		72.2	5.8	22	≤8	>32		
Ceftriaxone		67.1	6.5	26.4	≤0.06	>64		
Imipenem		99.3	0.7	0	0.25	0.5		
Levofloxacin		81.6	2.2	16.2	0.06	>8		
Minocycline		80.5	6.1	13.4	2	16		
Pip-Tazo		87.7	6.5	5.8	2	32		
<i>Klebsiella oxytoca</i> (n=57)		Tigecycline	100	0	0	0.25	0.5	
		Amikacin	100	0	0	2	4	
		Amox/Clav	75.4	7	17.5	4	32	
	Ampicillin	0	10.5	89.5	>32	>32		
	Cefepime	96.5	0	3.5	≤0.5	1		
	Ceftazidime	94.7	1.8	3.5	≤8	≤8		
	Ceftriaxone	91.2	5.3	3.5	≤0.06	8		
	Imipenem	100	0	0	0.25	0.5		
	Levofloxacin	89.5	1.8	8.8	0.03	4		
	Minocycline	96.5	1.8	1.8	1	2		
	Pip-Tazo	84.2	1.8	1.4	1	128		
	<i>S. marcescens</i> (n=122)	Tigecycline	97.5	0.8	1.6	1	2	
		Amikacin	94.3	0.8	4.9	2	8	
		Amox/Clav	0	5.7	94.3	>32	>32	
Ampicillin		0	4.1	95.9	>32	>32		
Cefepime		93.4	0	6.6	≤0.5	4		
Ceftazidime		88.5	0.8	10.7	≤8	32		
Ceftriaxone		87.7	4.1	8.2	0.25	32		
Imipenem		100	0	0	0.5	1		
Levofloxacin		94.3	2.5	3.3	0.12	0.5		
Minocycline		88.5	9	2.5	2	8		
Pip-Tazo		88.8	0	11.2	4	128		

*Species with n's <20 were omitted.
†Susceptibilities are defined by CLSI document M100-S16 (2006), where available. Tigecycline breakpoints defined by the FDA (Tygacil[®], 2005).

Table 2. In Vitro Activity of Tigecycline and Comparative Agents against *Acinetobacter baumannii* and *Pseudomonas aeruginosa*.

Organism	Drug	%Sus*	%Int	%Res	MIC (mcg/mL)			
					MIC ₅₀	MIC ₉₀	MIC ₉₉	
<i>Acinetobacter baumannii</i> (n=156)	Tigecycline	na	na	na	0.25	1		
	Amikacin	59.6	4.5	35.9	8	>64		
	Cefepime	45.5	5.8	48.7	16	>32		
	Ceftazidime	44.9	2.6	52.6	>32	>32		
	Ceftriaxone	25.6	21.2	53.2	64	>64		
	Imipenem	69.2	4.5	26.3	1	>16		
	Levofloxacin	51.9	20.5	27.6	2	8		
	Minocycline	92.3	7.1	0.6	≤0.5	4		
	Pip-Tazo	51.9	8.3	39.7	16	>128		
	<i>Pseudomonas aeruginosa</i> (n=294)	Tigecycline	na	na	na	8	>16	
		Amikacin	85.7	5.8	8.5	4	32	
Cefepime		70.4	11.2	18.4	4	32		
Ceftazidime		73.1	6.5	20.4	≤8	>32		
Ceftriaxone		11.6	27.2	61.2	64	>64		
Imipenem		81.4	7.6	11	1	16		
Levofloxacin		63.6	6.8	29.6	1	>8		
Minocycline	5.8	12.6	81.6	>16	>16			
Pip-Tazo	88.8	0	11.2	4	128			

*Susceptibilities are defined by CLSI document M100-S16 (2006), where available.
na = Breakpoints have not yet been established for tigecycline against these species.

Table 3. In Vitro Activity of Tigecycline and Comparative Agents against Non-fastidious Gram-positive Pathogens.

Organism	Drug	%Sus*	%Int	%Res	MIC (mcg/mL)			
					MIC ₅₀	MIC ₉₀	MIC ₉₉	
<i>S. aureus</i> (n=286)	Tigecycline	100	0	0	0.12	0.25		
	Amox-Clav	70.6	0	29.4	1	>8		
	Ampicillin	7.7	0	92.3	16	>16		
	Ceftriaxone	6.5	5.9	29	4	>64		
	Imipenem	76.4	0.7	22.9	0.25	>16		
	Levofloxacin	68.5	1.4	30.1	0.25	16		
	Linezolid	100	0	0	2	2		
	Minocycline	92.3	7.3	0.3	≤0.25	4		
	Penicillin	6.6	0	93.4	>8	>8		
	Pip-Tazo	70.3	0	29.7	1	>16		
	Vancomycin	100	0	0	1	1		
	<i>S. aureus</i> , MRSA (n=112)	Tigecycline	100	0	0	0.25	0.5	
		Amox-Clav	25	0	75	>8	>8	
		Ampicillin	0	0	100	>16	>16	
Ceftriaxone		13.4	12.5	74.1	>64	>64		
Imipenem		40.2	1.8	58	16	>16		
Levofloxacin		21.4	1.8	76.8				