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Tigecycline Evaluation Surveillance Trial (T.E.S.T.) Program - Australian Experience, 2006

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REVISED ABSTRACT

Background: Tigecycline, the first of a new antimicrobial class of glycylcyclines 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 three investigative sites in Australia. **Methods:** Minimum Inhibitory Concentration (MICs) of 500 clinical bacterial isolates collected during 2005 through 2006 were determined by broth microdilution and evaluated according to CLSI guidelines. **Results:** The broad-spectrum antimicrobials levofloxacin, cefepime, amikacin, and imipenem were highly active against Gram-negative strains (excluding *Pseudomonas*) in this study and demonstrated susceptible percentages rates of 97%, 96%, 93%, 98%, respectively. Tigecycline's activity was comparable to imipenem presenting an MIC_{90} value of 1 mcg/mL against all Gram-negative strains (excluding *Pseudomonas*). Tigecycline MIC_{90} was 0.12 mcg/mL against all gram-positive study isolates. Tigecycline MICs were 16- to 32-fold lower than 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* at a MIC of ≤0.5 mcg/mL regardless of methicillin phenotypes. Tigecycline inhibited all *H. influenzae* at ≤0.5 mcg/mL without regard to beta-lactamase production. **Conclusion:** Tigecycline's activity was comparable to the activities of broad spectrum antimicrobials and highly effective against 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 options 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 three medical centers in Australia.

INTRODUCTION

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylcyclines. 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 has been shown to be a highly effective agent against 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 MIC_{90} 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 clinical laboratory in vitro experience with activity of tigecycline in a limited number of clinical isolates collected from three medical centers in 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. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- 500 clinical isolates were collected and tested between January 2005 - December 2006 from three study centers from 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].
- Quality control of broth microdilution panels followed manufacture'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).

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RESULTS

The results of this study are presented in the following tables:

Table 1. Gram-negative Antibiogram for Tigecycline and 10 Comparators with MIC_{90} (mcg/mL) and Percent Susceptible (%) against 374 Selected Pathogens.

Gram-Negative Organisms	N=	MIC_{90} in mcg/mL (% Susceptible)* Tigecycline	Amikacin	AmoxClav	Ampicillin	Cefepime	Ceftazidime	Ceftriaxone	Imipenem	Levofloxacin	Minocycline	PipTazo
A. baumannii	27	2(na)	8(96.3)	>32(na)	>32(na)	>32(59.3)	>32(63)	>64(18.5)	>16(70.4)	>8(63)	8(74.1)	>128(63)
A. junii	1	0.12(na)	≤0.5(100)	0.5(na)	≤0.5(na)	≤0.5(100)	≤8(100)	4(100)	0.12(100)	0.12(100)	≤0.5(100)	≤0.06(100)
A. lwoffii	7	0.12(na)	2(100)	4(na)	8(na)	1(100)	≤8(100)	4(100)	0.25(100)	0.12(100)	≤0.5(100)	≤0.06(100)
A. spp	35	1(na)	8(97.1)	>32(na)	>32(na)	>32(68.6)	>32(71.4)	>64(37.1)	>16(77.1)	8(71.4)	8(80)	>128(71.4)
E. aerogenes	26	0.5(96.2)	2(100)	>32(0)	>32(0)	≤0.5(100)	32(65.4)	4(100)	1(100)	0.12(100)	4(96.2)	32(88.5)
E. cloacae	48	1(95.8)	4(100)	>32(2.1)	>32(0)	8(93.8)	>32(52.1)	>64(52.1)	1(100)	0.5(97.9)	8(85.4)	64(58.3)
E. gergoviae	1	0.5(100)	1(100)	16(0)	>32(0)	8(100)	>32(0)	32(0)	0.5(100)	0.12(100)	4(100)	128(0)
Enterobacteriaceae†	251	1(97.6)	4(100)	>32(49)	>32(15.5)	2(98.4)	32(84.9)	16(88.8)	1(100)	0.25(98.8)	4(91.2)	64(86.5)
E. coli	75	0.25(100)	8(100)	16(81.3)	>32(52)	≤0.5(100)	≤8(98.7)	0.12(100)	0.5(100)	0.06(98.7)	4(93.3)	2(97.3)
H. influenzae	28	0.5(na)	16(na)	2(100)	>32(82.1)	≤0.5(100)	≤8(na)	≤0.06(100)	1(100)	0.12(100)	1(na)	≤0.06(100)
H. influenzae (BL Neg)	24	0.5(na)	16(na)	1(100)	1(95.8)	<0.5(100)	≤8(na)	≤0.06(100)	1(100)	0.12(100)	1(na)	≤0.06(100)
H. influenzae (BL Pos)	4	0.25(na)	8(na)	4(100)	>32(0)	≤0.5(100)	≤8(na)	≤0.06(100)	2(100)	0.015(100)	≤0.5(na)	≤0.06(100)
K. oxytoca	29	0.5(100)	2(100)	32(72.4)	>32(0)	2(100)	≤8(96.6)	8(93.1)	0.5(100)	0.12(100)	2(100)	>128(75.9)
K. pneumoniae	42	1(97.6)	2(100)	4(92.9)	>32(0)	≤0.5(97.6)	≤8(95.2)	0.12(97.6)	0.5(100)	0.25(97.6)	4(92.9)	4(97.6)
K. pneumoniae, ESBL	1	1(100)	4(100)	16(0)	>32(0)	>32(0)	16(0)	>64(0)	0.25(100)	>8(0)	4(100)	8(100)
Klebsiella spp	71	1(98.6)	2(100)	32(84.5)	>32(0)	≤0.5(98.6)	≤8(95.8)	1(95.8)	0.5(100)	0.25(98.6)	4(95.8)	64(88.7)
P. aeruginosa	60	16(na)	16(95)	>32(0)	>32(na)	16(76.7)	16(86.7)	>64(8.3)	4(91.7)	8(76.7)	>16(3.3)	32(95)
S. marcescens	29	2(96.6)	8(100)	>32(0)	>32(0)	≤0.5(100)	≤8(96.6)	8(96.6)	2(100)	0.5(100)	8(82.8)	4(100)
S. odorifera	1	4(0)	2(100)	8(100)	32(0)	≤0.5(100)	≤8(100)	0.5(100)	0.5(100)	0.12(100)	8(0)	2(100)

* na = not applicable; breakpoint is undefined for this species/drug combination.
† *Enterobacter*, *Escherichia*, *Klebsiella* and *Serratia* combined.

Table 2. Gram-positive Antibiogram for Tigecycline and 10 Comparators with MIC_{90} (mcg/mL) and Percent Susceptible (%) against 126 Selected Pathogens.

Gram-Positive Organisms	N=	MIC_{90} in mcg/mL (% Susceptible)* Tigecycline	AmoxClav	Ampicillin	Ceftriaxone	Imipenem	Levofloxacin	Linezolid	Minocycline	Penicillin	PipTazo	Vancomycin
E. casseliflavus	1	0.12(100)	0.5(na)	0.5(100)	16(na)	0.5(na)	2(100)	2(100)	8(0)	0.5(100)	4(na)	4(100)
E. faecalis	27	0.12(100)	1(na)	1(100)	>64(na)	1(na)	32(77.8)	2(100)	>8(25.9)	4(100)	4(na)	2(100)
E. faecium	4	0.06(na)	>8(na)	>16(0)	>64(na)	>16(na)	>32(0)	2(100)	4(100)	>8(0)	>16(na)	2(100)
S. aureus	50	0.25(100)	>8(86)	>16(10)	>64(76)	0.5(92)	4(88)	2(100)	4(96)	>8(10)	>16(84)	1(100)
MSSA	40	0.25(100)	1(100)	16(12.5)	4(95)	0.25(100)	0.5(100)	2(100)	≤0.25(100)	>8(12.5)	2(100)	1(100)
MRSA	10	0.25(100)	>8(30)	>16(0)	>64(0)	>16(60)	4(40)	2(100)	8(80)	>8(0)	>16(20)	1(100)
S. agalactiae	17	0.06(100)	0.12(na)	0.12(100)	0.12(100)	0.25(na)	1(100)	2(100)	>8(na)	0.12(100)	0.5(na)	0.5(100)
S. pneumoniae	27	0.03(na)	1(100)	1(na)	1(96.3)	≤0.12(92)	1(100)	1(100)	4(na)	1(74.1)	1(na)	0.5(100)
Penicillin-Sus	20	0.03(na)	≤0.03(100)	≤0.06(na)	≤0.03(100)	≤0.12(100)	1(100)	1(100)	≤0.25(na)	≤0.06(100)	≤0.25(na)	0.5(100)
Penicillin-Inter	6	0.06(na)	1(100)	2(na)	2(83.3)	0.25(66.7)	2(100)	1(100)	>8(na)	1(0)	2(na)	0.5(100)
Penicillin-Res	1	0.015(na)	0.5(100)	1(na)	1(100)	≤0.12(100)	0.5(100)	1(100)	4(na)	2(0)	1(na)	0.5(100)

* na = not applicable; breakpoint is undefined for this species/drug combination.

Table 3. Frequency Distribution (n) and Cumulative Percents Inhibited (%) of Tigecycline against 500 Isolates of Selected Gram-negative and Gram-positive Pathogens.

Organism	N / Cum%	MIC (mcg/mL) 0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16
Acinetobacter baumannii	27			3	10	2	1	8	1	2			
				11.1	48.1	55.5	59.2	88.8	92.5	100			
Acinetobacter junii	1				1								
					100								
Acinetobacter lwoffii	7		1	3	3								
			14.3	57.2	100								
Enterobacter aerogenes	26					6	18		1	1			
						23.1	92.3	92.3	96.1	100			
Enterobacter cloacae	48					5	32	7	2		2		
						10.4	77.1	91.7	95.9	95.9	100		
Enterobacter gergoviae	1						1						
							100						
Enterococcus casseliflavus	1				1								
					100								
Enterococcus faecalis	27		1	9	17								
			3.7	37	100								
Enterococcus faecium	4		1	3									
			25	100									
Escherichia coli	75			1	48	24	2						
				1.3	65.3	97.3	100						
Haemophilus influenzae	28			1	10	13	4						
				3.6	39.3	85.7	100						
Klebsiella oxytoca	29					23	4	1	1				
						79.3	93.1	96.5	100				
Klebsiella pneumoniae	42					7	22	10	2	1			
						16.7	69.1	92.9	97.7	100			
Pseudomonas aeruginosa	60									6	28	23	3
										10	56.7	95	100
Serratia marcescens	29						1	19	8	1			
							3.4	68.9	96.5	100			
Serratia odorifera	1									1			
										100			
Staphylococcus aureus	50				41	8	1						
					82	98	100						
Streptococcus agalactiae	17			7	10								
				41.2	100								
Streptococcus pneumoniae	27	14	11	2									
		51.9	92.6	100									
Total for all Organisms:	500	14	21	32	131	88	86	45	15	12	30	23	3
		2.8	7	13.4	39.6	57.2	74.4	83.4	86.4	88.8	94.8	99.4	100

CONCLUSIONS

- Tigecycline inhibited 97.6% of all *Enterobacteriaceae* tested in vitro at a MIC_{90} of 1 mcg/mL. Tigecycline's MIC_{90} of 1 mcg/mL was equivalent to imipenem and 8- to 64-fold better than the beta-lactams and beta-lactam/beta-lactamase inhibitor combinations. Only levofloxacin had a lower MIC_{90} at 0.25 mcg/mL against all *Enterobacteriaceae* tested.
- Tigecycline showed potent activity against *A. baumannii* with the lowest MIC_{90} value of 2 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 MIC_{90} 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 0.5 mcg/mL.
- Tigecycline inhibited all *S. pneumoniae* at or below 0.06 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 these three Australian clinical laboratories against common gram-negative and gram-positive nosocomial and community acquired pathogens.