SR051

In Vitro Potency of Tigecycline Against Methicillin Resistant and Methicillin Sensitive Staphylococcus aureus Isolates from Asia and the Pacific Rim, 2004 - 2008

M. Renteria[1], J. Johnson[1], R. Badal[1], S. Hawser[1], M. Hackel[1], S. Bouchillon[1], B. Johnson[1], D. Hoban[1], M. Dowzicky[2]

[1]International Health Management Associates, Inc., Schaumburg, IL, USA
[2]Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL
60173
Tel: 847.303.5003
Fax: 847.303.5601

Revised Abstract

Objectives: Glycylcyclines are a new class of antimicrobials that show promise of significant activity against many gram-positive pathogens including *S. aureus*. Tigecycline, a member of this new class of antimicrobials, has shown excellent activity against *Staphylococcus* spp. This study was initiated to evaluate the in vitro activity of tigecycline as compared with those of 10 comparator agents (ampicillin, penicillin, imipenem, ceftriaxone, levofloxacin, minocycline, vancomycin, linezolid, amoxicillin/ clavulanic acid, and piperacillin-tazobactam) against *S. aureus* including methicillin- resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA) from study sites across Asia and the Pacific Rim as part of the T.E.S.T. program. **Methods**: A total of 1,302 clinical isolates were collected throughout 2004-2008 and MICs were determined by each participating center using broth microdilution. All testing was performed and interpreted according to CLSI guidelines and manufacturer's instructions. **Results**: Among the 1,302 isolates, 529 (40.6%) were found to be resistant to methicillin (MRSA). Besides the expected cross resistance of MRSA isolates to imipenem, ceftriaxone, penicillin, ampicillin, amoxicillin/clavulanic acid, and piperacillin/tazobactam, a high rate of non-susceptibility (I+R) to levofloxacin (74.1%) was observed. No resistance was observed against vancomycin and linezolid. The MICs of tigecycline ranged from 0.008 to 0.5 mcg/mL against all strains of *S. aureus*. Tigecycline presented the lowest MIC_{50}/MIC_{90} of 0.12/0.5 mcg/mL against MRSA strains, being several folds lower than all the comparator agents. The MSSA isolates showed the expected profile of high resistance to ampicillin and penicillin. Tigecycline's MIC_{50}/MIC_{90} of 0.12/0.25 mcg/mL was also the lowest among all MSSA isolates **Conclusions**: The inhibitory activity of tigecycline was complete for all *S. aureus* tested at its CLSI susceptible breakpoint of 0.5 mcg/ml regardless of methicillin phenotype. Tigecycline may be a therapeutic option against *S. aureus* including MRSA.

Introduction

Tigecycline is the first novel antimicrobial with an expanded broad-spectrum of activity from a new class of compounds, 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].

While developed to provide activity against tetracycline- and multi-drug-resistant gram-positive pathogens, it has been demonstrated to possess broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [1, 3-5]. Tigecycline MIC_{90} value of $\leq$0.5 mcg/mL have been demonstrated against methicillin-resistant *Staphylococcus aureus* (MRSA) [2, 4-6].

Tigecycline resistance is infrequent and difficult to induce in the laboratory [7, 8] with a selection frequency observed at less than 10^{-9} [2, 3, 7]. Most tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [1-4, 6, 9-11]. The pharmacokinetics of parenteral tigecycline is linear with an unusually long half-life of 36 hours [12].

This study compared the activity of tigecycline with other agents against methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA) in laboratories from 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.
- Clinical isolates were collected tested between January 2004 – December 2008 from 75 study centers in Australia, China, Hong Kong, India, Indonesia, Korea, Pakistan, Philippines, Singapore, and Taiwan.
- Antimicrobial agents tested with concentrations (expressed in mcg/mL) were: amoxicillin/clavulanic acid (0.03-8); piperacillin/tazobactam (0.25-16); levofloxacin (0.06-32); ceftriaxone (0.03-64); linezolid (0.5-8); minocycline (0.25-8); vancomycin (0.12-32); ampicillin (0.06-16); penicillin (0.06-8); tigecycline (0.008-16); imipenem (0.12-16) and meropenem (0.12-16). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute (CLSI) and FDA (Tygacil®, 2005) where applicable [13, 14].
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution. All MRSA and MSSA were confirmed by the central laboratory using oxacillin disk test (Oxoid).
- Quality control followed CLSI guidelines using quality control organism *S. aureus* ATCC 29213.
- The collection and transporting 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).

References

1 Sum, P.E. and P. Petersen, *Synthesis and structure-activity relationship of novel glycylcycline derivatives leading to the discovery of GAR-936.* Bioorg Med Chem Lett, 1999. **9**(10): p. 1459-62.

2 Abbanat, D., M. Macielag, 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 Betriu, 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 glycylcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates.* Diagn Microbiol Infect Dis, 2000. **36**(1): p. 19-36.

5 Milatovic, D., et al., *Activities of the Glycylcycline Tigecycline (GAR-936) against 1,924 Recent European Clinical Bacterial Isolates.* Antimicrob Agents Chemother, 2003. **47**(1): p. 400-4.

6 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.

7 Chopra, I., *New developments in tetracycline antibiotics: glycylcyclines and tetracycline efflux pump inhibitors.* Drug Resist Updat, 2002. **5**(3-4): p. 119-25.

8 Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycylcycline antibacterial agent.* Pharmacotherapy, 2000. **20**(9 Pt 2): p. 219S-223S; discussion 224S-228S.

9 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.

10 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.

11 Petersen, P.J., et al., *In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936).* Antimicrob Agents Chemother, 1999. **43**(4): p. 738-44.

12 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.

13 Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Eighteenth Informational Supplement. CLSI document M100-S18. Wayne, PA, 2008.

14 Tygacil®, FDA approved 2005. Product information, package insert. Wyeth Pharmaceuticals, Collegeville, PA, USA.

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Results

Table 1: In vitro activity of tigecycline and comparator agents against 1,302 Isolates of *Staphylococcus aureus.*

Organism	Drug	MIC (mcg/ml) MIC_{50}	MIC (mcg/ml) MIC_{90}	%Sus	%Int	%Res
S. aureus	Tigecycline	0.12	0.5	100	--	--
(n=1302)	AmoxClav	1	>8	61.1	0	38.9
	Ampicillin	16	>16	37.3	0	62.7
	Ceftriaxone	4	>64	59.9	3.4	36.7
	Imipenem	0.25	>16	55.9	0	44.1
	Levofloxacin	0.25	16	66.9	6.3	26.8
	Linezolid	2	2	100	0	0
	Meropenem	0.25	>16	71.5	2.0	26.5
	Minocycline	≤0.25	8	89.9	6.8	3.4
	Penicillin	>8	>8	36.6	0	63.4
	PipTazo	1	>16	62.6	0	37.4
	Vancomycin	1	1	100	0	0
S. aureus	Tigecycline	0.12	0.25	100	--	--
Methicillin-Susceptible	AmoxClav	1	2	100	0	0
(n=773)	Ampicillin	4	>16	62.7	0	37.3
	Ceftriaxone	2	4	98.8	0.6	0.5
	Imipenem	≤0.12	0.25	100	0	0.0
	Levofloxacin	0.12	0.5	95.2	3.8	1.0
	Linezolid	2	4	100	0	0
	Meropenem	≤0.12	0.25	99.8	0.2	0
	Minocycline	≤0.25	0.5	98.7	1.2	0.1
	Penicillin	8	>8	61.6	0	38.4
	PipTazo	1	2	100	0	0
	Vancomycin	1	1	100	0	0
S. aureus	Tigecycline	0.25	0.5	100	--	--
Methicillin-Resistant	AmoxClav	>8	>8	4.3	0	95.7
(n=529)	Ampicillin	>16	>16	0	0	100
	Ceftriaxone	>64	>64	3.0	7.4	89.6
	Imipenem	>16	>16	0	0	100
	Levofloxacin	8	32	25.9	9.6	64.5
	Linezolid	2	2	100	0	0.0
	Meropenem	16	>16	26.9	4.8	68.3
	Minocycline	2	8	76.9	14.9	8.1
	Penicillin	>8	>8	0	0	100
	PipTazo	>16	>16	7.9	0	92.1
	Vancomycin	1	1	100	0	0

[a] Breakpoints as defined by CLSI (M100-S18), 2008. Tigecycline breakpoints defined as: susceptible ≤ 0.5; intermediate and resistant are not defined (FDA, Tygacil®, 2005).

Table 2. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/mL) for tigecycline and comparative agents against 773 methicillin-sensitive *Staphylococcus aureus*.

N / Cumulative%	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥128
Tigecycline	2	1	4	96	474	172	24								
	0.3	0.4	0.9	13.3	74.6	96.9	100								
AmoxClav				4	39	73	194	352	103	8					
				0.5	5.6	15.0	40.1	85.6	99.0	100					
Ampicillin				31	48	19	45	75	105	90	123	109	128		
				4.0	10.2	12.7	18.5	28.2	41.8	53.4	69.3	83.4	100		
Ceftriaxone				1		2	1	32	361	337	24	10	1	2	2
				0.1		0.4	0.5	4.7	51.4	95.0	98.1	99.4	99.5	99.7	100
Imipenem					130	108	5	3	1						
					52.6	96.4	98.4	99.6	100						
Levofloxacin				60	356	256	38	12	16	28	3	3		1	
				7.8	53.8	86.9	91.8	93.4	95.5	99.1	99.5	99.9		100	
Linezolid							11	117	559	86					
							1.4	16.6	88.9	100					
Meropenem					402	96	15	6	3	3	1				
					76.4	94.7	97.5	98.7	99.2	99.8	100				
Minocycline						690	51	11	6	5	9	1			
						89.3	95.9	97.3	98.1	98.7	99.9	100			
Penicillin				69	12	20	60	54	76	79	113	290			
				8.9	10.5	13.1	20.8	27.8	37.6	47.9	62.5	100			
PipTazo						23	203	407	109	24	7				
						3.0	29.2	81.9	96.0	99.1	100				
Vancomycin					2	10	301	445	15						
					0.3	1.6	40.5	98.1	100						

* ≤ and > values for some drugs have been normalized by rounding up to the next highest MIC.

Table 3. Frequency distribution (n) and cumulative percent inhibition (%) at each MIC (mcg/mL) for tigecycline and comparative agents against 529 methicillin-resistant *Staphylococcus aureus*.

N / Cumulative%	≤0.008	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	≥128
Tigecycline	2	3	31	200	183	110								
	0.4	0.9	6.8	44.6	79.2	100								
AmoxClav					1	5	15	26	47	100	335			
					0.2	1.1	4.0	8.9	17.8	36.7	100			
Ampicillin						2	3	3	13	19	120	369		
						0.4	0.9	1.5	4.0	7.6	30.2	100		
Ceftriaxone							3	10	9	38	56	36	43	334
							0.6	2.5	4.2	11.3	21.9	28.7	36.9	100
Imipenem				7	28	13	6	6	8	4	23	100		
				3.6	17.9	24.6	27.7	30.8	34.9	36.9	48.7	100		
Levofloxacin			4	58	52	12	7	6	85	114	99	44	48	
			0.8	11.7	21.6	23.8	25.1	26.3	42.3	63.9	82.6	90.9	100	
Linezolid						15	151	320	43					
						2.8	31.4	91.9	100					
Meropenem				8	6	21	39	37	27	21	41	134		
				2.4	4.2	10.5	22.2	33.2	41.3	47.6	59.9	100		
Minocycline					219	25	16	46	101	79	43			
					41.4	46.1	49.1	57.8	76.9	91.9	100			
Penicillin						2	2	5	9	39	472			
						0.4	0.8	1.7	3.4	10.8	100			
PipTazo					1	5	17	26	26	46	48	360		
					0.2	1.1	4.3	9.3	14.2	22.9	31.9	100		
Vancomycin				3	3	156	334	32	1					
				0.6	1.1	30.6	93.8	99.8	100					

* ≤ and > values for some drugs have been normalized by rounding up to the next highest MIC.

Conclusions

- Tigecycline inhibited the growth of all MSSA and MRSA at a MIC $\leq$ 0.5 mcg/mL.
- Tigecycline demonstrates greater in vitro activity against MSSA and MRSA than levofloxacin, imipenem and the β-lactam antimicrobials.
- Tigecycline demonstrates in vitro activity comparable to commonly prescribed antimicrobial agents, linezolid and vancomycin, currently used for the treatment of serious staphylococcal nosocomial infections.
- Tigecycline may be a promising agent in the treatment of methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*.