Multicenter Retrospective Evaluation of Tigecycline Tested Against Clinical Pathogens from Japan (2003-2004)

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ABSTRACT

Background: In preparation for therapeutic use of tigecycline (first in class glycylcycline) in Japan, a retrospective sample of clinical isolates (2003-2004) was tested by the SENTRY Antimicrobial Surveillance Program. All tests were by reference methods.

Methods: Three university hospitals collected 1,033 pathogens for central laboratory processing by the CLSI procedures (fresh MH broth media) with concurrent quality control. Tigecycline and 23 comparators were tested including minocycline and tetracycline. Most numerous organisms were: staphylococci (303), enterococci (67), streptococci (194), *E. coli* (141), other Enterobacteriaceae (132), *H. influenzae* (73), *M. catarrhalis* (56) and *Acinetobacter* (16). Interpretive criteria were those of the US-FDA as published in the product package insert.

Results: Tigecycline MIC_{50} and susceptibility rates among species were identical between sampled years and more potent than either tetracycline or minocycline. The MIC_{90} range (mg/L)/% susceptible for ENT was 0.25-4/36-100 with lowest potency noted against *Proteae*. Amp-C (19-46%) and ESBL strains (4-12%) were tigecycline-susceptible (≤2 mg/L). Only 2 (*E. faecalis*) Gram-positive cocci (GPC; 0.3%) were tigecycline-non-susceptible at 2 mg/L. The MRSA and MR-coagulase-negative staphylococcal rates were 67 and 84%. No vancomycin-resistant enterococci and only one VISA strain was detected. *H. influenzae* (MIC_{90}, 0.5 mg/L; 40% ß-lactamase-negative ampicillin-resistant) and *M. catarrhalis* (MIC_{90}, 0.25 mg/L) were inhibited by tigecycline, as were all *Acinetobacter* strains at ≤4 mg/L (bimodal MIC distribution). Tigecycline was not active against *P. aeruginosa* (MIC_{90}, 32 mg/L).

	MIC (mg/L)		% by category:[a]	
Organism (no. tested)	50%	90%	Susceptible	Resistant
S. aureus (202)	0.12	0.5	100	0
CoNS (101)[b]	0.25	0.5	100	0
Enterococci (67)	0.12	0.25	97	-
Streptococci (194)	0.03	0.06	100	-
E. coli (141)	0.12	0.25	100	0
HI (73)	0.5	0.5	-	-
MCAT (56)	0.12	0.25	-	-
AC (16)	0.12	4	88[c]	0

a. Interpreted per US-FDA product package insert; - = no criteria.
b. CoNS = coagulase-negative staphylococci.
c. Per Jones et al. (2006).

Conclusions: Using US-FDA breakpoints, tigecycline-resistant rates among Japanese isolates were nil for Enterobacteriaceae and only 0.3% for GPC. Tigecycline appears to be active against current pathogens from Japan including prevalent resistance phenotypes (extended-spectrum ß-lactamases, MRSA, penicillin-resistant pneumococci).

INTRODUCTION

Tigecycline is a semisynthetic glycylcycline derived from minocycline that induces its bacteriostatic effect by binding to a high affinity intracellular site on the bacterial 30S-ribosome, thus blocking entry of amino-acyl tRNA molecules into the A site of the ribosome and preventing further protein synthesis. Tigecycline overcomes the two major determinants of tetracycline resistance: active efflux and protection of ribosomes.

Tigecycline is an important advance in treatment for a range of infections where mixed and/or resistant organisms play a role, and include a very broad spectrum comprising virtually all Gram-positive bacteria, most Gram-negative bacteria including anaerobes, and many strains harbouring resistance to other antimicrobial classes. In preparation for expanded clinical trials in Japan and the Asia-Pacific (APAC) region, the SENTRY Antimicrobial Surveillance Program retrospectively tested year 2003 and 2004 strains from Japan against tigecycline.

MATERIALS AND METHODS

Bacterial isolates. A total of 1,033 bacterial isolates collected during 2003-2004 in three medical centers located in Japan (Nagasaki University, Nagasaki; Kitasato University, Kanagawa; and Teikyo University, Tokyo) were evaluated as part of the SENTRY Antimicrobial Surveillance Program. The isolates were consecutively collected from bloodstream infections, skin and soft tissue infections, urinary tract infections and pneumonia in hospitalized patients according to a common protocol. Only isolates from documented infections were included in the study. Species identification was confirmed by standard biochemical tests and the Vitek System (bioMerieux, Hazelwood, MO), when necessary.

Antimicrobial susceptibility testing. All isolates were susceptibility tested using the broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI). Fresh cation-adjusted Mueller-Hinton broth was used in validated panels manufactured by TREK Diagnostics (Cleveland, OH). Categorical interpretations for comparator antimicrobials were those found in M100-S18; breakpoints for tigecycline were those of the United States (US) Food and Drug Administration (FDA). Quality control (QC) was performed using *Escherichia coli* ATCC 25922, *S. aureus* ATCC 29213 and *Pseudomonas aeruginosa* ATCC 27853; all QC results were within specified ranges as published in M100-S18. All strains were tested either at the Women's and Children's Hospital (Adelaide, Australia) or at JMI Laboratories (North Liberty, Iowa, USA).

Data were analyzed for MIC_{50}, MIC_{90} and percentage susceptible and resistant according to US-FDA tigecycline product labeling interpretive criteria (2005). Enterobacteriaceae with elevated MIC values (≥2 mg/L) for ceftazidime and/or ceftriaxone and/or aztreonam were considered as extended-spectrum ß-lactamase (ESBL)-producing phenotypes (see Table 2).

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RESULTS

- Tigecycline demonstrated remarkable activity at US-FDA breakpoints against Gram-positive organisms (MIC_{90} mg/L; % susceptible): *S. aureus* (0.5; 100.0), CoNS (0.5; 100.0), *E. faecalis* (0.25; 96.0), ß-haemolytic streptococci (0.06; 100.0) and viridans group streptococci (0.06; 100.0). *S. pneumoniae* interpretive criteria have not been established, but all tigecycline MIC results were at ≤0.25 mg/L (MIC_{90}, 0.06 mg/L; Table 1).
- Tigecycline activity against Enterobacteriaceae was excellent against indicated species including *C. freundii*, *Enterobacter* spp., *E. coli*, *Klebsiella* spp. and *S. marcescens* (MIC_{90} range, 0.25-2 mg/L); susceptibility rates were 96.2-100.0%. As noted here and cited in the US-FDA product package insert, "tigecycline has decreased in vitro activity against *Morganella* spp., *Proteus* spp. and *Providencia* spp." (Table 1).
- *H. influenzae* were inhibited by tigecycline at ≤2 mg/L, including 33 isolates that were ampicillin-resistant (only four produced ß-lactamase). BLNAR and BLN-amoxicillin/clavulanate-resistant strains are very common (45.2%) in Japan.
- *Acinetobacter* spp. had a bimodal MIC distribution for tigecycline e.g. 0.06-0.25 and 1-4 mg/L without resistance (0.0%) by US-FDA/Jones et al. definitions for Enterobacteriaceae.

Table 1. Summary of tigecycline activity tested by reference (CLSI) broth microdilution methods against 1,033 pathogens isolated in Japan (2003-2004; SENTRY Antimicrobial Surveillance Program).[a]

	Occurrences at MIC (mg/L) of:												MIC:		% by category:[b]	
Organism (no. tested)	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	50%	90%	Susceptible	Resistant
S. aureus (202)	1	2	20	86	61	32	0	0	0	0	0	0	0.12	0.5	100.0	0.0
CoNS (101)[c]	0	0	16	33	41	11	0	0	0	0	0	0	0.25	0.5	100.0	0.0
Enterococci (67)	0	1	14	30	20	2	0	0	0	0	0	0	0.12	0.25	97.0	-
E. faecalis (50)	0	1	11	22	14	2	0	0	0	0	0	0	0.12	0.25	96.0	-
ß-haemolytic streptococci (18)	1	14	3	0	0	0	0	0	0	0	0	0	0.03	0.06	100.0	-
S. pneumoniae (151)	2	104	43	1	1	0	0	0	0	0	0	0	0.03	0.06	100.0	-
Viridans group streptococci (25)	1	11	12	0	1	0	0	0	0	0	0	0	0.06	0.06	100.0	-
C. freundii (11)	0	0	0	0	8	3	0	0	0	0	0	0	0.25	0.5	100.0	0.0
Enterobacter spp. (26)	0	0	0	0	3	17	1	4	1	0	0	0	0.5	2	96.2	0.0
E. coli (141)	0	0	2	84	51	4	0	0	0	0	0	0	0.12	0.25	100.0	0.0
Klebsiella spp. (57)	0	0	0	0	14	36	4	3	0	0	0	0	0.5	1	100.0	0.0
K. pneumoniae (52)	0	0	0	0	13	32	4	3	0	0	0	0	0.5	1	100.0	0.0
Proteus mirabilis (11)	0	0	0	0	0	0	0	4	7	0	0	0	4	4	36.4	0.0
Indole-positive *Proteae* (11)	0	0	0	0	0	1	7	3	0	0	0	0	1	2	100.0	0.0
S. marcescens (16)	0	0	0	0	0	4	11	1	0	0	0	0	1	1	100.0	0.0
H. influenzae (73)	0	0	0	7	23	40	2	1	0	0	0	0	0.5	0.5	-	-
M. catarrhalis (56)	0	0	6	33	17	0	0	0	0	0	0	0	0.12	0.25	-	-
Acinetobacter spp. (16)[d]	0	0	1	7	3	0	2	1	2	0	0	0	0.12	4	87.5[d]	0.0
P. aeruginosa (51)	0	0	0	0	0	0	1	0	5	22	15	8	8	32	-	-

a. Three medical centers participated in this program (Nagasaki, Teikyo, and Kitasato).
b. Susceptibility criteria published by the US-FDA (2005).
c. CoNS = coagulase-negative staphylococcal species.
d. Criteria from Jones et al. (2007), same as US-FDA breakpoint criteria for Enterobacteriaceae.

Table 2. Comparative antimicrobial activity of tigecycline compared to selected antimicrobials tested against pathogens with sample sizes of ≥50 isolates (2003-2004).

		MIC (mg/L)		% by category:[a]				MIC (mg/L)		% by category:[a]	
Organism (no. tested)	Antimicrobial agent	50%	90%	Susceptible	Resistant	Organism (no. tested)	Antimicrobial agent	50%	90%	Susceptible	Resistant
S. aureus (252)	Tigecycline	0.5	0.5	100.0	-[b]	*H. influenzae* (73)	Tigecycline	0.5	0.5	-	-
	Minocycline	≤0.25	>8	65.3	31.7		Tetracycline	≤2	≤2	97.3	2.7
	Oxacillin	>2	>2	32.7	67.3		Ampicillin	1	48	54.8	26.0[c]
	Erythromycin	>8	>8	25.7	74.3		A/C[b]	2	0.25	75.3	24.7[c]
	Levofloxacin	4	>4	34.7	64.9		Ceftriaxone	0.015	≤0.03	100.0	-
	TMP/SMX[b]	≤0.5	≤0.5	100.0	0.0		Levofloxacin	≤0.03	4	100.0	-
	Vancomycin	1	2	99.5	0.0		TMP/SMX	≤0.5	4	89.0	11.0
CoNS (101)[b]	Tigecycline	0.25	0.5	100.0	-	*M. catarrhalis* (56)	Tigecycline	0.12	0.25	-	-
	Minocycline	≤0.25	0.5	97.0	2.0		Minocycline	≤0.25	≤0.25	-	-
	Oxacillin	>2	>2	15.8	84.2		A/C	0.25	1	-	-
	Erythromycin	>8	>8	29.7	70.3		Ceftriaxone	0.5	1	-	-
	Levofloxacin	4	>4	34.7	51.5		Levofloxacin	≤0.03	0.06	-	-
	TMP/SMX	≤0.5	>2	73.3	26.7		TMP/SMX	≤0.5	≤0.5	-	-
	Vancomycin	2	2	100.0	0.0	*E. coli* (141)	Tigecycline	0.12	0.25	100.0	0.0
Enterococci (67)	Tigecycline	0.12	0.25	97.0	-		Minocycline	1	8	85.8	5.7
	Minocycline	8	>8	40.3	38.8		Ceftriaxone	≤0.25	≤0.25	97.9	2.1
	Ampicillin	≤1	>16	80.6	19.4		P/T[b]	2	2	98.6	0.7
	Chloramphenicol	8	>16	85.1	14.9		Imipenem	≤0.5	≤0.5	100.0	0.0
	Levofloxacin	1	>4	65.7	34.3		Gentamicin	≤2	4	90.1	9.9
	Vancomycin	1	2	100.0	0.0		Levofloxacin	≤0.03	>4	83.7	12.8
S. pneumoniae (151)	Tigecycline	0.03	0.06	-	-	*Klebsiella* spp. (57)	Tigecycline	0.5	1	100.0	0.0
	Minocycline	8	>8	-	-		Minocycline	2	>8	75.4	14.0
	Penicillin	0.25	4	31.8	35.1		Ceftriaxone	≤0.25	>32	87.7	10.5 (12.3)[d]
	Ceftriaxone	1	2	88.7	2.0		P/T	4	8	96.5	3.5
	Erythromycin	>8	>8	18.5	80.8		Imipenem	≤0.5	≤0.5	100.0	0.0
	Clindamycin	>2	>2	44.4	55.6		Gentamicin	≤2	≤2	94.7	5.3
	Levofloxacin	1	1	99.3	0.7		Levofloxacin	0.06	0.25	96.5	3.5
	TMP/SMX	≤0.5	2	62.9	9.9						
	Vancomycin	0.5	0.5	100.0	-						

a. CLSI interpretive criteria except for tigecycline (US-FDA, 2005).
b. - = no interpretive criteria have been published. TMP/SMX = trimethoprim/sulfamethoxazole, CoNS = coagulase-negative staphylococci, A/C = amoxicillin/clavulanate, P/T = piperacillin/tazobactam.
c. Evidence of ß-lactamase-negative ampicillin-resistant isolates.
d. Percentage ESBL phenotype.

CONCLUSIONS

- When reference tested against 1,033 Japanese isolates from 2003-2004, tigecycline was very active against Gram-positive cocci (all MIC values at ≤0.5 mg/L).
- Tigecycline was also active against most Enterobacteriaceae at ≤2 mg/L and all strains had MIC values at ≤4 mg/L (Table 1).
- Tigecycline appears to be a promising glycylcycline for use in Japan, including application against isolates having resistances to other antimicrobial classes.