480

Antimicrobial Activity of Tigecycline and Comparator Agents Tested Against Gram-Positive Organisms Collected in the Asia-Pacific Region in 2006

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ABSTRACT

Background:

Tigecycline (TGC) is a novel glycylcycline recently approved by the US-FDA for treatment of cutaneous and intra-abdominal infections. We assessed the activity of TGC against recent Gram-positive (GP) organisms collected on 42 medical centers (9 countries).

Methods:

3,177 bacterial isolates (non-duplicates) were consecutively collected in 2006 from documented infections in patients hospitalized from (no. of centers; strains): Australia (5; 660), China (11; 993), Hong Kong (1; 101), India (11; 584), Indonesia (4; 60), Korea (3; 274), Philippines (2; 135), Singapore (1; 121), Taiwan (2; 129) and Thailand (2; 120). The isolates were susceptibility (S) tested in a central laboratory (Adelaide, Australia) using CLSI broth microdilution methods and guidelines. TGC-S breakpoints were defined as ≤0.5 µg/ml for staphylococci and ≤0.25 µg/ml for streptococci and enterococci following interpretive criteria established by the US-FDA.

Results:

TGC was highly active against all GP species tested with 99.6% S overall (Table). Only 2 *S. aureus* (0.12%), 2 coagulase-negative staphylococci (CoNS; 0.6%) and 10 enterococci (1.5%) were non-S to TGC, all with TGC MIC only one doubling dilution above the S breakpoint. Oxacillin resistance (R) was observed on 41.9% of *S. aureus* and 83.6% of CoNS. Among *E. faecium*, 90.2 and 71.7% were S to vancomycin and quinupristin/dalfopristin, respectively. *S. pneumoniae* showed low S to tetracycline (29.5%), erythromycin (34.1%), clindamycin (38.7%), penicillin (62.1%) and ceftriaxone (81.2%), but levofloxacin remained very active (98.5% S).

Organism (no. tested)	Cumulative % at TGC MIC (µg/ml) value of[a]: ≤0.03	0.06	0.12	0.25	0.5	1
Oxacillin-S *S. aureus* (957)	0.5	23.5	75.0	99.4	<u>100.0</u>	-
Oxacillin-R *S. aureus* (689)	0.3	8.4	47.6	89.0	<u>99.7</u>	100.0
Oxacillin-S CoNS (55)	7.3	20.0	67.1	<u>100.0</u>	-	-
Oxacillin-R CoNS (280)	0.4	10.4	44.3	85.7	<u>99.3</u>	100.0
E. faecalis (379)	0.0	10.6	64.1	<u>97.9</u>	100.0	-
E. faecium (265)	9.8	46.8	91.7	<u>99.2</u>	100.0	-
Other *Enterococcus* spp. (30)	0.0	26.7	70.0	<u>100.0</u>	-	-
S. pneumoniae (261)	98.1	99.6	<u>100.0</u>	-	-	-
ß-haemolytic streptococci (172)	79.7	95.3	99.4	<u>100.0</u>	-	-
Viridans group streptococci (89)	87.6	94.4	96.6	<u>100.0</u>	-	-

a. Underline values indicate % S.

Conclusions:

TGC exhibited a wide-spectrum of activity and potency against GP organisms collected in the Asia-Pacific region, including multidrug-R isolates.

INTRODUCTION

Tigecycline, a glycylcycline derived from the minocycline molecule, has recently been approved by the United States (USA)-Food and Drug Administration (FDA). Its broad-spectrum includes documented activity against many Gram-negative and Gram-positive pathogens including Enterobacteriaceae, *Acinetobacter* spp., methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, penicillin-resistant *Streptococcus pneumoniae*, anaerobic wound infection pathogens, *Neisseria gonorrhoeae*, and commonly occurring respiratory pathogens. Tigecycline has documented activity against tigecycline-resistant (tet-R) Gram-positive and Gram-negative pathogens refractory to therapy by both efflux and ribosomal protection mechanisms. In addition, tigecycline does not show cross-resistance to other antimicrobial classes.

Although contemporary tetracycline derivatives such as doxycycline and minocycline display an increased spectrum of activity and favorable pharmacokinetics compared with tetracycline, cross-resistance within the class persists. The glycylcyclines have the distinct advantage of enhanced stability to the major tetracycline resistance mechanisms, specifically an increased binding affinity to Tet (M)- and Tet (O)-protected tetracycline-resistant ribosomes and secondarily through the inhibition of tetracycline efflux determinants, and have been major advancements.

In the present study, we evaluated the activity of tigecycline and select comparators tested against Gram-positive organisms from the Asia-Pacific region.

MATERIALS AND METHODS

<u>Bacterial Isolates</u>: A total 3,177 bacterial isolates (non-duplicates) were consecutively collected in 2006 from documented infections in patients hospitalized in the following countries (no. of centers; strains): Australia (5; 660), China/Hong Kong (11/1; 993/101), India (11; 584), Indonesia (4; 60), Korea (3; 274), Philippines (2; 135), Singapore (1; 121), Taiwan (2; 129) and Thailand (2; 120). All isolates were identified by the participant laboratories and confirmed by the monitoring facility.

<u>Susceptibility Testing</u>: MIC values were determined for tigecycline and comparator agents at a central laboratory (Adelaide, Australia) using validated, dry-form broth microdilution panels with cation-adjusted Mueller-Hinton medium. Testing, incubation and MIC interpretations were performed using the recommendations of the Clinical and Laboratory Standards Institute (CLSI; formerly NCCLS) and the manufacturer. Tigecycline susceptible (S) breakpoints were defined as ≤0.5 µg/ml for staphylococci and ≤0.25 µg/ml for streptococci and enterococci, as approved by the USA-FDA. Quality control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619.

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RESULTS

- Tigecycline was very active against staphylococci (MIC_{50}, 0.12 – 0.25 µg/ml) and showed antimicrobial spectrum similar to that of linezolid and vancomycin (>99% susceptibility) against *S. aureus* and coagulase-negative staphylococci (Tables 1 and 2).
- Only two *S. aureus* (0.3%) and two CoNS (0.6%) strains were considered non-susceptible to tigecycline; all with tigecycline MIC of 1 µg/ml, only one dilution above the susceptible breakpoint established by the USA-FDA (≤0.5 µg/ml; Table 1).

Table 1. Tigecycline MIC distributions of Gram-positive organisms isolates in the Asia-Pacific Region.

Organism (no. tested)	No. of strains (cumulative %) inhibited at tigecycline MIC (µg/ml) of: ≤0.03	0.06	0.12	0.25	0.5	1	2	4
S. aureus (1,646)	7 (0.4)	276 (17.2)	763 (63.5)	518 (95.0)	80 (99.9)	2 (100.0)	-	-
MSSA (957)	5 (0.5)	220 (23.5)	493 (75.0)	233 (99.4)	6 (100.0)	-	-	-
MRSA (689)	2 (0.3)	56 (8.4)	270 (47.6)	285 (89.0)	74 (99.7)	2 (100.0)	-	-
CoNS (335)	5 (1.5)	35 (11.9)	121 (48.1)	134 (88.1)	38 (99.4)	2 (100.0)	-	-
MS-CoNS (55)	4 (7.3)	7 (20.0)	26 (67.1)	18 (100.0)	-	-	-	-
MR-CoNS (280)	1 (0.4)	28 (10.4)	95 (44.3)	116 (85.7)	38 (99.3)	2 (100.0)	-	-
Enterococcus spp. (674)	26 (3.9)	146 (25.5)	335 (75.2)	157 (98.5)	10 (100.0)	-	-	-
E. faecalis (379)	0 (0.0)	40 (10.6)	203 (64.1)	128 (97.9)	8 (100.0)	-	-	-
E. faecium (265)	26 (9.8)	98 (46.8)	119 (91.7)	20 (99.2)	2 (100.0)	-	-	-
S. pneumoniae (261)	256 (98.1)	4 (99.6)	1 (100.0)	-	-	-	-	-
ß-haemolytic streptococci (172)	137 (79.7)	27 (95.3)	7 (99.4)	1 (100.0)	-	-	-	-
Group A (63)	58 (92.1)	4 (98.4)	1 (100.0)	-	-	-	-	-
Group B (77)	64 (83.1)	13 (100.0)	-	-	-	-	-	-
Viridans group streptococci (89)	78 (87.6)	6 (94.4)	2 (96.6)	3 (100.0)	-	-	-	-

Table 2. Antimicrobial activity of tigecycline and selected comparator agents tested against Gram-positive organisms collected in the Asia-Pacific region.

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
S. aureus				
Oxacillin-susceptible (957)				
Tigecycline[b]	0.12	0.25	≤0.03-0.5	100.0 / -
Tetracycline	≤2	>8	≤2->8	83.8 / 15.9
Erythromycin	≤0.25	>2	≤0.25->2	73.8 / 26.1
Clindamycin	≤0.25	>2	≤0.25->2	88.7 / 11.3
Levofloxacin	≤0.5	4	≤0.5->4	88.5 / 11.1
Trim/sulfa[e]	≤0.5	1	≤0.5->2	93.0 / 7.0
Linezolid	2	2	0.5-4	100.0 / -
Vancomycin	1	1	0.5-2	100.0 / 0.0
Oxacillin-resistant (689)				
Tigecycline[b]	0.25	0.5	≤0.03-1	99.7 / -
Tetracycline	>8	>8	≤2->8	32.9 / 67.1
Erythromycin	>2	>2	≤0.25->2	13.8 / 85.5
Clindamycin	>2	>2	≤0.25->2	45.0 / 55.0
Levofloxacin	>4	>4	≤0.5->4	16.5 / 82.6
Trim/sulfa[e]	≤0.5	>2	≤0.5->2	60.4 / 39.6
Linezolid	1	2	0.5-4	100.0 / -
Vancomycin	1	2	0.5-4	99.6 / 0.0
CoNS				
Oxacillin-susceptible (55)				
Tigecycline[c]	0.12	0.25	≤0.03-0.25	100.0 / -
Tetracycline	≤2	>8	≤2->8	81.8 / 18.2
Erythromycin	≤0.25	>2	≤0.25->2	83.6 / 16.4
Clindamycin	≤0.25	≤0.25	≤0.25->2	98.2 / 1.8
Levofloxacin	≤0.5	1	≤0.5->4	92.7 / 7.3
Trim/sulfa[e]	≤0.5	>2	≤0.5->2	87.3 / 12.7
Linezolid	1	1	0.25-1	100.0 / -
Vancomycin	1	2	0.25-2	100.0 / 0.0
Oxacillin-resistant (280)				
Tigecycline[c]	0.25	0.5	≤0.03-1	99.4 / -
Tetracycline	≤2	>8	≤2->8	80.4 / 19.6
Erythromycin	>2	>2	≤0.25->2	28.2 / 71.4
Clindamycin	≤0.25	>2	≤0.25->2	73.9 / 18.6
Levofloxacin	4	>4	≤0.5->4	35.4 / 59.6
Trim/sulfa[e]	1	>2	≤0.5->2	55.4 / 44.6
Linezolid	1	1	0.12->8	99.6 / -
Vancomycin	2	2	0.25-4	100.0 / 0.0

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
E. faecalis (379)				
Tigecycline[d]	0.12	0.25	0.06-0.5	97.9 / -
Tetracycline	>8	>8	≤2->8	23.5 / 76.5
Ampicillin	≤1	2	≤1-8	100.0 / 0.0
Levofloxacin	1	>4	≤0.5->4	63.6 / 36.1
Gentamicin (HL)	≤500	>1000	≤500->1000	53.6 / 46.4
Streptomycin (HL)	≤1000	>2000	≤1000->2000	60.7 / 39.3
Linezolid	1	2	0.5-8	99.7 / 0.3
Vancomycin	1	2	1->16	99.7 / 0.3
E. faecium (265)				
Tigecycline[d]	0.12	0.12	≤0.03-0.5	99.2 / -
Tetracycline	≤2	>8	≤2->8	60.8 / 37.7
Ampicillin	>16	>16	≤1->16	5.7 / 94.3
Levofloxacin	>4	>4	≤0.5->4	9.4 / 87.9
Gentamicin (HL)	>1000	>1000	≤500->1000	27.5 / 72.5
Streptomycin (HL)	≤1000	>2000	≤1000->2000	54.7 / 45.3
Linezolid	1	2	1-4	98.5 / 0.0
Vancomycin	1	4	0.5->16	90.2 / 9.8
Enterococcus spp. (30)				
Tigecycline[d]	0.12	0.25	0.06-0.25	100.0 / -
Tetracycline	≤2	>8	≤2->8	76.7 / 23.3
Ampicillin	≤1	≤1	≤1-4	100.0 / 0.0
Levofloxacin	1	2	≤0.5->4	90.0 / 10.0
Gentamicin (HL)	≤500	≤500	≤500->1000	93.3 / 6.7
Streptomycin (HL)	≤1000	≤1000	≤1000->2000	93.3 / 6.7
Linezolid	2	2	1-4	96.7 / 0.0
Vancomycin	2	4	0.5-8	90.0 / 0.0
Streptococcus pneumoniae (261)				
Tigecycline[d]	≤0.03	≤0.03	≤0.03-0.12	100.0 / -
Tetracycline	>8	>8	≤2->8	29.5 / 69.7
Erythromycin	>2	>2	≤0.25->2	34.1 / 65.9
Clindamycin	>2	>2	≤0.25->2	38.7 / 61.3
Penicillin	0.03	4	≤0.015-32	62.1 / 28.0
Ceftriaxone	≤0.25	2	≤0.25-32	81.2 / 6.1
Levofloxacin	1	1	≤0.5->4	98.5 / 1.5
Trim/sulfa[e]	>2	>2	≤0.5->2	36.0 / 53.6
Linezolid	1	1	0.25-2	100.0 / -
Vancomycin	0.5	0.5	≤0.12-1	100.0 / -

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
ß-haemolytic streptococci (172)				
Tigecycline[b]	≤0.03	0.06	≤0.03-0.25	100.0 / -
Tetracycline	>8	>8	≤2->8	33.7 / 62.8
Erythromycin	≤0.25	>2	≤0.25->2	74.4 / 25.0
Clindamycin	≤0.25	>2	≤0.25->2	79.1 / 20.9
Penicillin	≤0.015	0.06	≤0.015-0.12	100.0 / -
Ceftriaxone	≤0.25	≤0.25	≤0.25-0.5	100.0 / -
Levofloxacin	≤0.5	1	≤0.5->4	98.8 / 1.2
Trim/sulfa[e]	≤0.5	≤0.5	≤0.5->2	- / -
Linezolid	1	1	0.25-2	100.0 / -
Vancomycin	0.5	0.5	0.25-1	100.0 / -
Viridans group streptococci (89)				
Tigecycline[b]	≤0.03	0.06	≤0.03-0.25	100.0 / -
Tetracycline	8	>8	≤2->8	46.1 / 50.6
Erythromycin	≤0.25	>2	≤0.25->2	62.9 / 37.1
Clindamycin	≤0.25	>2	≤0.25->2	85.4 / 14.6
Penicillin	0.12	2	≤0.015-8	60.7 / 2.2
Ceftriaxone	≤0.25	1	≤0.25-4	92.1 / 2.2
Levofloxacin	1	1	≤0.5->4	96.6 / 3.4
Trim/sulfa[e]	≤0.5	>2	≤0.5->2	- / -
Linezolid	1	1	0.25-2	100.0 / -
Vancomycin	0.5	1	≤0.12-1	100.0 / -

a. Criteria as published by the CLSI [2007], ß-lactam susceptibility should be directed by the oxacillin test results.
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2005].
c. Susceptible breakpoint established by the USA-FDA for *S. aureus* (≤0.5 µg/ml) was applied for comparison purposes.
d. Susceptible breakpoint established by the USA-FDA for *E. faecalis* and streptococci other than *S. pneumoniae* (≤0.25 µg/ml) was applied for comparison purposes.
e. Trimethoprim/sulfamethoxazole

- Oxacillin-resistant staphylococci showed tigecycline MIC values slightly higher (two-fold) than oxacillin-susceptible strains (Table 1).
- *E. faecalis* showed high rates of susceptibility to many antimicrobials, including ampicillin (100.0%), linezolid (99.7%), vancomycin (99.7%) and tigecycline (97.9%; MIC_{90}, 0.25 µg/ml). In contrast, *E. faecium* generally showed high rates of resistance with the most active compounds being tigecycline (MIC_{90}, 0.12 µg/ml; 99.2% susceptible) and linezolid (MIC_{90}, 2 µg/ml; 98.5% susceptible).
- *E. faecium* (MIC_{90}, 0.12 µg/ml) exhibited tigecycline MIC values slightly lower compared to *E. faecalis* (MIC_{90}, 0.25 µg/ml; Table 1).
- Tigecycline (MIC_{90}, ≤0.03 µg/ml; 100% inhibited at ≤0.12 µg/ml), vancomycin (MIC_{90}, 1 µg/ml; 100.0% susceptible) and linezolid (MIC_{90}, 1 µg/ml; 100.0% susceptible) were the most active compounds tested against *S. pneumoniae.* Tigecycline was the most potent among those compounds (Tables 1 and 2).
- Tigecycline was also very active against ß-haemolytic and viridians group streptococci (MIC_{90}, 0.06 µg/ml; 100.0% susceptible; Tables 1 and 2).

CONCLUSIONS

- Tigecycline was very active against Gram-positive organisms collected in the Asia-Pacific region, and appears to be a valuable treatment option for serious infections caused by these pathogens, including multidrug-resistant organisms.
- Longitudinal surveillance programs are of great importance in monitoring the in vitro activity of novel compounds following their introduction into clinical practice.