479

Assessment of Tigecycline and Other Broad-Spectrum Agents Activities Tested Against Enterobacteriaceae from the Asia-Pacific Region (2006)

HS SADER, RN JONES, TR FRITSCHE, JM BELL, JD TURNIDGE

JMI Laboratories, North Liberty, IA, USA; Women's and Children's Hospital, N. Adelaide, Australia

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

ABSTRACT

Background:

We assessed the spectrum and potency of the novel glycylcycline tigecycline (TGC) against recent Enterobacteriaceae (ENT) collected from hospitals located in 9 countries.

Methods:

2,270 clinically significant ENT isolates (one per patient) were consecutively collected in 2006 and susceptibility (S) tested at a central laboratory (Adelaide, Australia) by CLSI broth microdilution methods. The isolates were from Australia, China, Hong Kong, India, Indonesia, Korea, Philippines, Singapore, Taiwan and Thailand. TGC breakpoints were ≤2 µg/ml for S and ≥8 µg/ml for resistant (R), as approved by the US-FDA for indicated ENT species. *E. coli*, *K. pneumoniae* (KPN) and *P. mirabilis* (PM) isolates with decreased S (MIC, ≥2 µg/ml) for ceftriaxone or ceftazidime were considered an ESBL phenotype and had antibiograms analyzed separately.

Results:

TGC was very active against *Citrobacter* spp., *E. coli* (EC), *Klebsiella* spp. (KSP), *Enterobacter* spp., and *Salmonella* spp. with $MIC_{50/90}$ of 0.25-0.5/0.5-1 µg/ml and 99-100% S. All *Serratia* spp. had TGC MIC at ≤2 µg/ml. ESBL phenotypes were observed among 54% of EC and 52% of KPN, and TGC was active against 100.0 and 98.4%, respectively. High R rates to ciprofloxacin (CIP) and gentamicin (GEN) were observed among EC (62.6 and 46.9% respectively) and KSP (35.6 and 38.9%). Among ESBL-phenotype strains, R rates to CIP and GEN were 77.2 and 66.7% for EC, respectively and 60.3 and 74.3% for KPN.

Organism (no. tested)	Cumulative % at TGC MIC (µg/ml) value of[a]: ≤0.12	0.25	0.5	1	2	4	>4
Citrobacter spp. (59)	6.8	69.5	93.2	100.0	-	-	-
E. coli (781)	36.5	86.5	99.6	100.0	-	-	-
Klebsiella spp. (794)	1.1	33.5	78.0	95.7	99.1	99.7	100.0
Enterobacter spp. (308)	0.3	22.4	83.4	94.2	99.0	100.0	-
Indole-positive Proteae (61)	0.0	1.6	8.2	52.5	88.5	100.0	-
P. mirabilis (92)	0.0	0.0	1.1	18.5	65.2	98.9	100.0
Serratia spp. (91)	0.0	0.0	33.0	91.2	100.0	-	-
Salmonella spp. (76)	19.7	67.1	98.7	100.0	-	-	-

a. Underline values indicate % S (US-FDA criteria for indicated species).

Conclusions:

ENT collected in the Asia-Pacific region showed high rates of R to commonly used broad-spectrum agents. However, the most frequently isolated species were S to TGC. TGC represents a reasonable therapeutic option for ENT infections in this geographic area, especially those caused by ESBL-producing and/or MDR strains.

INTRODUCTION

Tigecycline is a novel semisynthetic glycylcycline derived from the minocycline molecule approved by the United States Food and Drug Administration (USA-FDA) and by the European Medicines Agency (EMEA) for the treatment of complicated skin and skin structure and complicated intra-abdominal infections.

This novel compound has documented activity against tetracycline-resistant (tet-R) Gram-positive and Gram-negative pathogens refractory by both efflux and ribosomal protection mechanisms. Tigecycline has also shown in vitro activity against multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and carbapenem-resistant Enterobacteriaceae and *Acinetobacter* spp.

We assessed the spectrum and potency of tigecycline tested against recent Enterobacteriaceae collected from hospitals located in 9 countries in Asia-Pacific region.

MATERIALS AND METHODS

Bacterial Isolates: A total of 2,270 clinically significant Enterobacteriaceae isolates (one per patient) were consecutively collected in 2006. The isolates were from (no. of medical centers): Australia (5), China (11), Hong Kong (1), India (11), Indonesia (4), Korea (3), Philippines (2), Singapore (1), Taiwan (2) and Thailand (2). Species identification was performed by the participant laboratories and confirmed by the monitoring facility when necessary.

Susceptibility Testing: Each strain was tested by a reference broth microdilution method against more than 30 antimicrobial agents at a central laboratory (Adelaide, Australia). Only selected agents with the widest potential clinical utility and in vitro activity are reported here. Interpretation of quantitative MIC results was in accordance with Clinical and Laboratory Standards Institute (CLSI) methods and criteria. Tigecycline susceptible breakpoints were defined as ≤2 µg/ml for Enterobacteriaceae, as approved by the USA-FDA. *E. coli*, *K. pneumoniae* and *P. mirabilis* isolates with decreased susceptibility (MIC, ≥2 µg/ml) to ceftriaxone or ceftazidime were considered an ESBL phenotype. Current quality control testing was performed using the following organisms: *Escherichia coli* ATCC 25923; *Pseudomonas aeruginosa* 27853 and *Staphylococcus aureus* ATCC 29213.

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RESULTS

- Tigecycline showed excellent activity against *E. coli* (MIC_{90}, 0.5 µg/ml; 100.0% susceptible) and it was equally active against the subset of strains with ESBL-phenotype compared to the entire *E. coli* collection (Table 1).
- Similarly, tigecycline MIC distribution was not adversely affected by ESBL-phenotype among *Klebsiella* spp. (MIC_{90}, 1 µg/ml; 98.4-99.1% susceptible; Table 1).

Table 1. Tigecycline MIC distributions for Enterobacteriaceae from the APAC 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	>4
E. coli (781)	1 (0.1)	27 (3.6)	257 (36.5)	394 (86.9)	99 (99.6)	3 (100.0)	-	-	-
E. coli ESBL-positive (421)[a]	0 (0.0)	6 (1.0)	111 (27.3)	237 (83.6)	67 (99.5)	2 (100.0)	-	-	-
K. pneumoniae (744)	0 (0.0)	0 (0.0)	4 (0.5)	229 (31.3)	338 (76.7)	140 (95.6)	26 (99.1)	5 (99.7)	2 (100.0)
K. pneumoniae ESBL-positive (385)[a]	0 (0.0)	0 (0.0)	1 (0.3)	77 (20.3)	188 (69.1)	97 (94.3)	16 (98.4)	4 (99.5)	2 (100.0)
P. mirabilis (92)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	16 (18.5)	60 (65.2)	14 (98.9)	1 (100.0)
P. mirabilis ESBL-positive (24)[a]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (37.5)	14 (95.8)	1 (100.0)	-
Citrobacter spp. (59)	0 (0.0)	1 (1.7)	3 (6.8)	37 (69.5)	14 (93.2)	4 (100.0)	-	-	-
C. freundii (36)	0 (0.0)	1 (2.8)	2 (8.3)	22 (69.4)	8 (91.7)	3 (100.0)	-	-	-
Enterobacter spp. (308)	0 (0.0)	0 (0.0)	1 (0.3)	68 (22.4)	183 (83.4)	33 (94.2)	15 (99.0)	3 (100.0)	-
E. cloacae (236)	0 (0.0)	0 (0.0)	0 (0.0)	45 (19.1)	153 (83.9)	25 (94.5)	11 (99.2)	2 (100.0)	-
Indole-positive Proteae (61)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	4 (8.2)	27 (52.5)	22 (88.5)	7 (100.0)	-
P. vulgaris (18)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	9 (61.1)	6 (94.4)	1 (100.0)	-
Providencia stuartii (10)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (30.0)	7 (100.0)	-	-
Serratia spp. (91)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (33.0)	53 (91.2)	8 (100.0)	-	-
S. marcescens (85)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	27 (31.8)	51 (91.8)	7 (100.0)	-	-
Salmonella spp. (76)	0 (0.0)	0 (0.0)	15 (19.7)	36 (67.1)	24 (98.7)	1 (100.0)	-	-	-
S. paratyphi (22)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.1)	19 (95.5)	1 (100.0)	-	-	-
S. typhi (43)	0 (0.0)	0 (0.0)	14 (32.6)	26 (60.5)	3 (100.0)	-	-	-	-

a. Isolates with ESBL-phenotypes.

Table 2. Antimicrobial activity of tigecycline and selected comparators tested against Enterobacteriaceae collected in the Asia-Pacific region.

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
E. coli (781)				
Tigecycline[b]	0.25	0.5	≤0.03-1	100.0 / 0.0
Tetracycline	>8	>8	≤2->8	30.7 / 68.4
Piperacillin/tazobactam	2	16	≤0.5->64	90.1 / 4.9
Ceftriaxone	>32	>32	≤0.25->32	47.8 / 50.6
Ceftazidime	≤1	>16	≤1->16	71.3 / 16.6
Imipenem	0.25	0.25	≤0.12->8	99.9 / 0.1
Levofloxacin	>4	>4	≤0.5->4	37.8 / 58.4
Gentamicin	≤2	>8	≤2->8	52.0 / 46.9
E. coli ESBL-positive (421)				
Tigecycline[b]	0.25	0.5	0.06-1	100.0 / 0.0
Tetracycline	>8	>8	≤2->8	18.1 / 81.2
Piperacillin/tazobactam	8	32	≤0.5->64	84.8 / 7.6
Ceftriaxone	>32	>32	≤0.25->32	3.1 / 93.8
Ceftazidime	16	>16	≤1->16	46.8 / 30.9
Imipenem	0.25	0.25	≤0.12->8	99.8 / 0.2
Levofloxacin	>4	>4	≤0.5->4	13.1 / 82.2
Gentamicin	>8	>8	≤2->8	31.6 / 66.7
Klebsiella spp. (794)				
Tigecycline[b]	0.5	1	0.06->4	99.1 / 0.3
Tetracycline	≤2	>8	≤2->8	59.4 / 38.0
Piperacillin/tazobactam	4	>64	≤0.5->64	74.1 / 13.1
Ceftriaxone	≤0.25	>32	≤0.25->32	53.4 / 42.8
Ceftazidime	≤1	>16	≤1->16	62.0 / 30.0
Imipenem	0.25	0.5	≤0.12->8	99.6 / 0.3
Levofloxacin	≤0.5	>4	≤0.5->4	68.3 / 27.8
Gentamicin	≤2	>8	≤2->8	60.2 / 38.9
K. pneumoniae ESBL-positive (385)				
Tigecycline[b]	0.5	1	0.12->4	98.4 / 0.5
Tetracycline	>8	>8	≤2->8	36.9 / 60.8
Piperacillin/tazobactam	16	>64	1->64	50.6 / 26.0
Ceftriaxone	>32	>32	≤0.25->32	7.3 / 85.2
Ceftazidime	>16	>16	≤1->16	23.4 / 60.8
Imipenem	0.25	1	≤0.12->8	99.2 / 0.5
Levofloxacin	4	>4	≤0.5->4	44.4 / 49.4
Gentamicin	>8	>8	≤2->8	24.7 / 74.3

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
Proteus mirabilis (92)				
Tigecycline[b]	2	4	0.5->4	83.7 / 1.1
Tetracycline	>8	>8	≤2->8	5.4 / 94.6
Piperacillin/tazobactam	≤0.5	2	≤0.5-16	100.0 / 0.0
Ceftriaxone	≤0.25	>32	≤0.25->32	81.5 / 16.3
Ceftazidime	≤1	>16	≤1->16	80.4 / 19.6
Imipenem	2	4	0.5-8	97.8 / 0.0
Levofloxacin	1	>4	≤0.5->4	63.0 / 25.0
Gentamicin	≤2	>8	≤2->8	67.4 / 27.2
P. mirabilis ESBL-positive (24)				
Tigecycline[b]	2	2	1-4	95.8 / 0.0
Tetracycline	>8	>8	4->8	8.3 / 91.7
Piperacillin/tazobactam	≤0.5	4	≤0.5-16	100.0 / 0.0
Ceftriaxone	>32	>32	1->32	29.2 / 62.5
Ceftazidime	>16	>16	≤1->16	25.0 / 75.0
Imipenem	2	4	1-8	95.8 / 0.0
Levofloxacin	4	>4	≤0.5->4	41.7 / 41.7
Gentamicin	8	>8	≤2->8	33.3 / 50.0
Citrobacter spp. (59)				
Tigecycline[b]	0.25	0.5	0.06-1	100.0 / 0.0
Tetracycline	≤2	>8	≤2->8	66.1 / 33.9
Piperacillin/tazobactam	4	>64	≤0.5->64	76.3 / 10.2
Ceftriaxone	≤0.25	>32	≤0.25->32	62.7 / 28.8
Ceftazidime	≤1	>16	≤1->16	64.4 / 30.5
Imipenem	0.5	1	≤0.12-2	100.0 / 0.0
Levofloxacin	≤0.5	>4	≤0.5->4	83.1 / 11.9
Gentamicin	≤2	>8	≤2->8	71.2 / 28.8
Enterobacter spp. (308)				
Tigecycline[b]	0.5	1	0.12-4	99.0 / 0.0
Tetracycline	≤2	>8	≤2->8	59.4 / 38.3
Piperacillin/tazobactam	4	>64	≤0.5->64	72.4 / 14.9
Ceftriaxone	8	>32	≤0.25->32	50.3 / 39.0
Ceftazidime	8	>16	≤1->16	53.9 / 38.3
Imipenem	0.5	2	≤0.12->8	99.7 / 0.3
Levofloxacin	≤0.5	>4	≤0.5->4	78.9 / 15.3
Gentamicin	≤2	>8	≤2->8	62.0 / 36.0

Organism (no. tested)/ antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/ resistant[a]
Indole-positive Proteae (61)				
Tigecycline[b]	1	4	0.25-4	88.5 / 0.0
Tetracycline	>8	>8	≤2->8	26.2 / 67.2
Piperacillin/tazobactam	≤0.5	4	≤0.5->64	95.1 / 1.6
Cefoxitin	8	16	≤2->16	72.1 / 8.2
Ceftriaxone	≤0.25	>32	≤0.25->32	83.6 / 13.1
Ceftazidime	≤1	>16	≤1->16	82.0 / 13.1
Cefepime	≤0.12	16	≤0.12->16	88.5 / 9.8
Imipenem	2	4	0.5-8	98.4 / 0.0
Levofloxacin	≤0.5	>4	≤0.5->4	72.1 / 23.0
Gentamicin	≤2	>8	≤2->8	72.1 / 26.2
Serratia spp. (91)				
Tigecycline[b]	1	1	0.5-2	100.0 / 0.0
Tetracycline	>8	>8	4->8	2.2 / 75.8
Piperacillin/tazobactam	2	16	≤0.5->64	92.3 / 2.2
Ceftriaxone	≤0.25	16	≤0.25->32	89.0 / 5.5
Ceftazidime	≤1	≤1	≤1->16	95.6 / 2.2
Imipenem	1	2	0.25->8	98.9 / 1.1
Levofloxacin	≤0.5	1	≤0.5->4	95.6 / 3.3
Gentamicin	≤2	>8	≤2->8	86.8 / 13.2
Salmonella spp. (76)				
Tigecycline[b]	0.25	0.5	0.12-1	100.0 / 0.0
Tetracycline	≤2	4	≤2->8	96.1 / 3.9
Piperacillin/tazobactam	2	4	1-4	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25->32	98.7 / 1.3
Ceftazidime	≤1	≤1	≤1-8	100.0 / 0.0
Levofloxacin	≤0.5	1	≤0.5->4	98.7 / 1.3
Gentamicin	≤2	≤2	≤2-8	98.7 / 0.0

a. Criteria as published by the CLSI [2007].
b. USA-FDA breakpoints for indicated Enterobacteriaceae species were applied [Tygacil Product Insert, 2005].

- *Citrobacter* spp. (MIC_{90}, 0.5 µg/ml; 100.0% susceptible), *Salmonella* spp. (MIC_{90}, 0.5 µg/ml), *Serratia* spp. (MIC_{90}, 1 µg/ml) and *Enterobacter* spp. (MIC_{90}, 1 µg/ml; 99.0% susceptible) were very susceptible to tigecycline. *P. mirabilis* (MIC_{90}, 4 µg/ml) and indole-positive Proteae (MIC_{90}, 4 µg/ml) exhibited slightly higher tigecycline MIC values (Table 1).
- The prevalence of isolates with ESBL phenotype was extremely high among *E. coli* (53.9%), *Klebsiella* spp. (51.7%) and *P. mirabilis* (26.1%).
- High resistance rates to levofloxacin and gentamicin were observed among *E. coli* (58.4 and 46.9% respectively) and *Klebsiella* spp. (27.8 and 38.9%). Among ESBL-phenotype strains, resistance rates to levofloxacin and gentamicin were 82.2 and 66.7% for *E. coli*, respectively and 49.4 and 74.3% for *K. pneumoniae*.
- *Klebsiella* spp. (794 strains; 35.0%), *E. coli* (781; 34.4%) and *Enterobacter* spp. (308; 13.6%) were the most frequently isolated pathogens. They represented 83.0% of the collection and the most active compounds against these organisms were tigecycline (99.0-100.0% susceptible) and imipenem (99.2-99.9%; Table 2).
- Among those agents tested against *E. coli*, the rank order of susceptibility was: tigecycline (MIC_{90}, 0.5 µg/ml, 100.0% susceptible) > imipenem (99.9% susceptible) > ceftazidime (71.3%) > gentamicin (52.0%). The only agents that displayed > 75% susceptibility to *E. coli* strains with ESBL-phenotype were tigecycline (100.0%) and imipenem (99.8%; Table 2).
- The rank order of susceptibility among agents tested against *Klebsiella* spp. was: imipenem (99.6%) > tigecycline (99.1%) > piperacillin/tazobactam (74.1%) > levofloxacin (68.3%) > ceftazidime (62.0%) > gentamicin (60.2%). Among strains with ESBL-phenotype, only imipenem (99.2%) and tigecycline (98.4%) displayed significant activity; no other agent had ≥ 51% susceptibility (Table 2).

CONCLUSIONS

- Enterobacteriaceae collected in the Asia-Pacific region showed high rates of resistance to commonly used broad-spectrum agents. However, the most frequently isolated species were susceptible to tigecycline.
- High prevalence of strains with ESBL-phenotype and resistance to levofloxacin and gentamicin was observed among Enterobacteriaceae strains causing infections in this region.
- Due to its excellent antimicrobial spectrum, tigecycline represents an important option for teatment of Enterobacteriaceae infections in the Asia-Pacific region, especially those caused by ESBL-producing and/or MDR strains.