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Spectrum and Potency of Tigecycline Tested Against Non-Enteric Gram-negative Bacilli Collected Across the Asia-Pacific Region (2006)

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ABSTRACT

Background:

Resistance (R) among non-enteric Gram-negative bacilli (NEGN) to carbapenems and other broad-spectrum agents is a global concern with few new antimicrobials entering development. The novel glycylcycline tigecycline (TGC) and comparator agents were tested against NFGN recently collected in 2006 from 42 hospitals located in Australia and Asia.

Methods:

Bacterial isolates (one per patient) of clinical significance were collected (prevalence format) and tested for susceptibility (S) by CLSI broth microdilution methods in a central laboratory. TGC breakpoints approved by the US-FDA for indicated Gram-negative species (≥2 µg/ml for S and ≥8 µg/ml for resistant [R]) were used for comparison purposes only.

Results:

A total of 1,269 strains from respiratory tract (51%), skin/soft tissue (28%) and bloodstream (22%) infections were evaluated. TGC was the most active compound overall (Table). TGC was very active against all species evaluated except *P. aeruginosa*. *A. baumannii* showed very high R rates to all antimicrobials, except TGC and polymyxin B (PB). PB was the only agent with reasonable activity against *P. aeruginosa*, but showed limited activity against *Aeromonas* spp., *B. cepacia* and *S. maltophilia*. Ceftazidime (CAZ), imipenem (IMP), ciprofloxacin (CIP) and amikacin (AMK) showed limited activity against the most prevalent NFGN.

Organisms (no. tested)	MIC$_{50}$ (µg/ml) / % S					
	TGC	CAZ	IMP	CIP	AMK	PB[a]
A. baumannii (484)	0.5/98.6	>16/34.9	4/56.8	>4/34.1	>32/41.3	≤0.5/99.6
Aeromonas spp. (14)	0.25/100.0	≤1/92.9	1/92.9	0.12/100.0	≤4/100.0	1/64.3
A. xylosoxidans (14)	0.5/100.0	4/92.9	2/84.7	2/14.3	>32/7.1	2/84.7
B. cepacia (30)	1/80.0	4/93.3	8/23.3	1/50.0	>32/0.0	>4/0.0
M. catarrhalis[b] (22)	0.06/100.0	≤1/100.0	≤0.12/100.0	≤0.03/100.0	≤4/100.0	1/100.0
P. aeruginosa (556)	>4/2.3	4/57.6	2/72.1	0.5/54.0	≤4/69.6	1/99.6
S. maltophilia (115)	0.5/98.3	>16/32.2	>8/0.0	2/15.7	>32/8.7	>4/25.2

a. CLSI S breakpoints for *Acinetobacter* spp. and *P. aeruginosa* were applied for all pathogens.
b. CLSI breakpoints for Enterobacteriaceae were applied.

Conclusions:

TGC showed excellent in vitro activity against NEGN isolated in patients hospitalized in the Asia-Pacific region evaluated, including strains MDR to antimicrobials currently used to treat these infections. TGC seems to represent an important complimentary addition to the few remaining parenteral agents active against this emerging pathogens.

INTRODUCTION

Dramatic increases in the prevalence multidrug-resistant non-enteric Gram-negative bacilli are changing the face of empiric antimicrobial therapy in health care settings that deal with a high proportion of seriously ill patients, often with co-morbidities. Resistance to "third"- and "fourth-generation" cephalosporins, ß-lactam/ß-lactamase inhibitor combinations, and even carbapenems has become common in various geographic regions, requiring the utilization of unproven antimicrobial regimens or 'agents of last resort', such as polymyxin B and colistin. New agents to combat these resistant pathogens are sorely needed.

Tigecycline is the first member of the glycylcycline class approved by the United States Food and Drug Administration (USA-FDA) as a parenteral agent for the treatment of complicated skin and skin structure and intra-abdominal infections. Although chemically related to the tetracyclines and displaying identical binding sites on the 30S ribosomal subunit, tigecycline binds to the target much more avidly and offers enhanced stability to the usual tetracycline efflux and ribosomal protection resistance mechanisms.

In the present study, we evaluated the activity of tigecycline and comparator agents tested against non-enteric Gram-negative bacilli collected in 2006 from 42 hospitals located in Australia and Asia.

MATERIALS AND METHODS

Bacterial Isolates: A total of 1,269 strain clinically significant 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 Methods: MIC values for tigecycline and comparator agents were tested using validated, dry-form broth microdilution panels (TREK Diagnostics, Cleveland, OH) with fresh cation-adjusted Mueller-Hinton broth medium. Testing, incubation and MIC interpretations were performed using the manufacturers recommendations and suggested technical details of the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS).Tigecycline susceptibility breakpoint interpretations as defined by the USA-FDA for Enterobacteriaceae (≤2 µg/ml is susceptible, 4 µg/ml is intermediate and ≥8 µg/ml resistant) were applied to the non-enteric Gram-negative species presented for comparison purposes only.

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RESULTS

- The strains were collected mainly from respiratory tract (51%), skin and soft tissue (28%) and bloodstream (22%) infections.
- *A. baumannii* complex showed very high resistance rates to all antimicrobials, except tigecycline (MIC$_{90}$, 1 µg/ml; 98.6% susceptible) and polymyxin B (MIC$_{90}$, 1 µg/ml; 99.6% susceptible).
- Tigecycline was highly active against *Acinetobacter* spp. (MIC$_{90}$, 0.25-1 µg/ml), *Aeromonas* spp. (MIC$_{50}$, 0.5 µg/ml), *A. xylosoxidans* (MIC$_{50}$, 2 µg/ml), *M. catarrhalis* (MIC$_{50}$, 0.12 µg/ml) and *S. maltophilia* (MIC$_{50}$, 2 µg/ml). In contrast, *Pseudomonas* spp. (*P. aeruginosa* and *P. putida*) and *B. cepacia* showed higher tigecycline MIC values (Table 1).
- Imipenem (MIC$_{50}$, 4 µg/ml) and amikacin (MIC$_{50}$, >32 µg/ml) were active against only 56.8 and 41.3% of *Acinetobacter baumannii* complex strains at the respective susceptible breakpoints.
- Polymyxin B was the only agent with reasonable activity against *P. aeruginosa* (MIC$_{90}$, 2 µg/ml; 99.6% susceptible) but showed limited activity against *Aeromonas* spp. (MIC$_{90}$, >4 µg/ml; 64.3% susceptible), *B. cepacia* (MIC$_{50}$, >4 µg/ml; 0.0% susceptible) and *S. maltophilia* (MIC$_{50}$, >4 µg/ml; 25.2% susceptible; Table 2).
- Tigecycline and minocycline were the most active compounds tested against *S. maltophilia* (MIC$_{90}$, 1 µg/ml; 98.3% susceptible for both), followed by trimethoprim/sulfamethoxazole (MIC$_{90}$, ≤0.5 µg/ml; 87.8% susceptible) and levofloxacin (MIC$_{90}$, 1 µg/ml; 86.1% susceptible).
- Ceftazidime, imipenem, ciprofloxacin and amikacin showed limited activity against the most prevalent non-enteric Gram-negative bacilli (Table 2).

Table 1. Tigecycline MIC distributions for non-enteric Gram-negative bacilli from the Asia-Pacific region (2006).

Organism (no. tested)	No. of strains (% cumulative) inhibited at tigecycline MIC (µg/ml) at:							
	≤0.06	0.12	0.25	0.5	1	2	4	>4
A. baumannii complex (484)	31 (6.4)	82 (23.3)	72 (38.2)	141 (67.4)	134 (95.0)	17 (98.6)	6 (99.8)	1 (100.0)
A. junii (10)	1 (10.0)	7 (80.0)	1 (90.0)	1 (100.0)	-	-	-	-
A lwoffii (12)	3 (25.0)	2 (41.7)	4 (75.0)	3 (100.0)	-	-	-	-
Aeromonas spp. (14)	0 (0.0)	0 (0.0)	9 (64.3)	4 (92.9)	1 (100.0)	-	-	-
A. xylosoxidans (14)	0 (0.0)	1 (7.1)	0 (7.1)	7 (57.1)	4 (85.7)	2 (100.0)	-	-
B. cepacia (30)	0 (0.0)	0 (0.0)	2 (6.7)	11 (43.3)	6 (63.3)	5 (80.0)	4 (93.3)	2 (100.0)
M. catarrhalis (22)	16 (72.7)	22 (100.0)	-	-	-	-	-	-
P. aeruginosa (556)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	8 (2.3)	71 (15.1)	472 (100.0)
P. putida (12)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0	1 (8.3)	5 (50.0)	8 (66.7)	4 (100.0)
S. maltophilia (115)	0 (0.0)	2 (1.7)	14 (13.9)	57 (63.5)	32 (91.3)	8 (98.3)	1 (99.1)	1 (100.0)

Table 2. Antimicrobial activity of tigecycline and selected antimicrobial agents tested against non-enteric Gram-negative bacilli collected in the Asia-Pacific region.

Organism (no. tested)/ antimicrobial agent	MIC$_{50}$	MIC$_{90}$	Range	% susceptible/ resistant[a]
Acinetobacter baumannii complex (484)				
Tigecycline[b]	0.5	1	≤0.03->4	98.6 / 0.2
Tetracycline	>8	>8	≤2->8	38.0 / 57.0
Ampicillin/sulbactam	>16	>16	≤2->16	39.7 / 54.5
Ceftazidime	>16	>16	≤1->16	34.9 / 62.8
Imipenem	4	>8	≤0.12->8	56.8 / 39.5
Levofloxacin	>4	>4	≤0.5->4	36.0 / 52.1
Ciprofloxacin	>4	>4	≤0.03->4	34.1 / 65.5
Gentamicin	>8	>8	≤2->8	32.4 / 66.7
Amikacin	>32	>32	≤4->32	41.3 / 56.6
Polymyxin B	≤0.5	1	≤0.5->4	99.6 / 0.4
Aeromonas spp. (14)				
Tigecycline[b]	0.25	0.5	0.25-1	100.0 / 0.0
Tetracycline	≤2	>8	≤2->8	64.3 / 35.7
Piperacillin/tazobactam	8	>64	2->64	50.0 / 28.6
Ceftazidime	≤1	8	≤1->16	92.9 / 7.1
Imipenem	1	2	≤0.12->8	92.9 / 7.1
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / 0.0
Ciprofloxacin	0.12	0.5	≤0.03-0.5	100.0 / 0.0
Gentamicin	≤2	≤2	≤2	100.0 / 0.0
Amikacin	≤4	≤4	≤4-16	100.0 / 0.0
Polymyxin B[c]	1	>4	≤0.5->4	64.3 / 35.7
Achromobacter xylosoxidans (14)				
Tigecycline[b]	0.5	2	0.12-2	100.0 / 0.0
Tetracycline	>8	>8	≤2->8	7.1 / 85.7
Piperacillin/tazobactam	≤0.5	16	≤0.5-16	100.0 / 0.0
Ceftazidime	4	8	≤1-16	92.9 / 0.0
Imipenem	2	>8	1->8	85.7 / 14.3
Levofloxacin	2	4	≤0.5-4	78.6 / 0.0
Ciprofloxacin	2	4	1->4	14.3 / 42.9
Gentamicin	>8	>8	>8	0.0 / 100.0
Amikacin	>32	>32	8->32	7.1 / 92.9
Polymyxin B[c]	2	4	≤0.5->4	85.7 / 14.3
Burkholderia cepacia (30)				
Tigecycline[b]	1	4	0.25->4	80.0 / 6.7
Tetracycline	>8	>8	8->8	- / -
Piperacillin/tazobactam[c]	4	32	2-64	100.0 / 0.0
Ceftazidime	4	8	2-16	93.3 / 0.0
Imipenem[c]	8	8	2->8	23.3 / 10.0
Meropenem	2	8	1->8	86.7 / 6.7
Levofloxacin	2	>4	≤0.5->4	73.3 / 13.3
Ciprofloxacin[c]	1	4	0.5->4	50.0 / 3.3
Amikacinc	>32	>32	32->32	0.0 / 93.3
Polymyxin B[c]	>4	>4	>4	0.0 / 100.0
Trimethoprim/sulfamethoxazole	≤0.5	1	≤0.5->2	96.7 / 3.3
Minocycline	2	>8	≤1->8	76.7 / 13.3

Organism (no. tested)/ antimicrobial agent	MIC$_{50}$	MIC$_{90}$	Range	% susceptible/ resistant[a]
Moraxella catarrhalis (22)				
Tigecycline[b]	0.06	0.12	≤0.03-0.12	100.0 / 0.0
Tetracycline	≤2	≤2	≤2	- / -
Ampicillin/sulbactam	≤2	≤2	≤2	- / -
Piperacillin/tazobactam	≤0.5	≤0.5	≤0.5	- / -
Ceftazidime	≤1	≤1	≤1	- / -
Imipenem	≤0.12	≤0.12	≤0.12-0.25	- / -
Ciprofloxacin	≤0.03	≤0.03	≤0.03-0.06	- / -
Gentamicin	≤2	≤2	≤2	- / -
Polymyxin B	1	1	≤0.5-2	- / -
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	- / -
Pseudomonas aeruginosa (556)				
Tigecycline[b]	>4	>4	1->4	2.3 / 84.9
Tetracycline	>8	>8	≤2->8	0.9 / 97.3
Piperacillin/tazobactam	16	>64	≤0.5->64	71.2 / 28.8
Ceftazidime	4	>16	≤1->16	57.6 / 38.3
Imipenem	2	>8	≤0.12->8	72.1 / 25.9
Levofloxacin	2	>4	≤0.5->4	53.1 / 43.5
Ciprofloxacin	0.5	>4	≤0.03->4	54.0 / 42.6
Gentamicin	≤2	>8	≤2->8	60.1 / 38.5
Amikacin	≤4	>32	≤4->32	69.6 / 28.1
Polymyxin B	1	2	≤0.5->4	99.6 / 0.4
Stenotrophomonas maltophilia (115)				
Tigecycline[b]	0.5	1	0.12->4	98.3 / 0.9
Tetracycline	>8	>8	4->8	- / -
Ceftazidime	>16	>16	≤1->16	32.2 / 52.2
Levofloxacin	1	4	≤0.5->4	86.1 / 6.1
Polymyxin B[c]	>4	>4	≤0.5->4	25.2 / 64.3
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5->2	87.8 / 12.2
Ticarcillin/clavulanate	64	>128	≤16->128	33.0 / 34.8
Minocycline	≤1	2	≤1->8	98.3 / 0.9

a. Criteria as published by the CLSI [2007].
b. Breakpoints established for Enterobacteriaceae by the USA-FDA were applied for comparison purposes.
c. Breakpoint established by the CLSI for *P. aeruginosa* was applied for comparison purpose.

CONCLUSIONS

- Tigecycline showed excellent in vitro activity against non-enteric Gram-negative bacilli isolated in patients hospitalized in the Asia-Pacific region including strains resistant to antimicrobials currently used to treat these infections.
- Tigecycline seems to represent an important complimentary addition to the few remaining parenteral agents active against some of these emerging pathogens.