Antimicrobial Activity of Tigecycline Tested Against Contemporary Bacterial Isolates Collected in Australia (2006)

JM BELL, JD TURNIDGE, RN JONES, MJ DOWZICKY

Women's and Children's Hosp., Adelaide, Australia; JMI Laboratories, North Liberty, IA; Wyeth Pharmaceuticals, Collegeville, PA

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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: Tigecycline has been marketed in Australia for over one year. As part of the SENTRY Antimicrobial Surveillance Program (Asia-Pacific Region), we evaluated the activity of tigecycline against recent (2006) bacterial isolates across Australia.

Methods: Non-duplicate strains were consecutively collected from five medical centres in 5 states using isolates from bacteraemia (n=253), pneumonia (n=146), complicated skin and skin structure infections (n=264), and other infections (n=269). All isolates were tested against tigecycline using validated commercial reference broth microdilution panels (TREK Diagnostics), with concurrent quality controls and CLSI (M100-S18) interpretations for comparison agents. Tigecycline breakpoints published by the US-FDA were applied for each indicated species or genus group.

Results: A total of 932 (268 Gram-negative and 664 Gram-positive) isolates were processed. Tigecycline was highly active against the top 10 non-pseudomonal pathogens which comprised 88% of all tested isolates (see Table). Tigecycline MIC_{90} results ranged from ≤0.12 to 1 mg/L, highest for *Klebsiella* spp. and *Proteae* (data not shown). At US-FDA published breakpoints, tigecycline exhibited complete inhibition of indicated species except for a single strain of *E. cloacae* (MIC, 4 mg/L). Over 28% of *Staphylococcus aureus* were oxacillin-resistant, and one *Enterococcus faecium* was vancomycin-resistant. Tigecycline was highly effective against these strains.

Conclusions: Tigecycline has potent activity against all the common pathogens isolated in 2006 from Australian patients, including those resistant to other drug classes. Documented acquired resistance was rare among indicated pathogens, however, *Pseudomonas* remains refractory to potential tigecycline therapy.

INTRODUCTION

Tigecycline is an important advance in treatment for a range of infections where mixed and/or resistant organisms play a role. It is able to bypass standard mechanisms of tetracycline resistance, and hence has a very broad spectrum that includes virtually all Gram-positive bacteria, most Gram-negative bacteria including anaerobes, and many strains harbouring resistance to other antimicrobial classes. Tigecycline was launched in Australia in mid-2006, at a time when tetracycline resistance was known to be very common amongst almost all important human pathogens. At the time of its launch, we investigated its activity against a full range of pathogens isolated from hospitalised patients with serious infections.

MATERIALS AND METHODS

Bacterial isolates: Non-duplicate clinically significant patient isolates were submitted from five medical centres from five states of Australia. Species identification of all isolates was confirmed in a central laboratory (Women's and Children's Hospital, Adelaide, Australia) using reference methodologies.

Susceptibility tests: Isolates were tested against tigecycline using validated broth microdilution MIC panels with cation-adjusted Mueller-Hinton broth (TREK Diagnostic Systems; East Grinstead, UK). Testing and incubation were performed using the manufacturer's recommendations and/or reference Clinical and Laboratory Standards Institute (CLSI) methods (2006). MIC tests were performed in cation-adjusted Mueller-Hinton broth (with the addition of 2-5% lysed horse blood for testing of streptococci). Quality control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619; all MIC results were within CLSI specified ranges.

Analysis: MIC interpretation was performed using the manufacturer's recommendations and/or reference CLSI interpretative criteria (2008). Tigecycline MIC results were interpreted using the US-FDA package insert (2005) in the absence of CLSI breakpoints.

RESULTS

- A total of 932 (268 Gram-negative and 644 Gram-positive) isolates were processed. Results for the top ten non-pseudomonal pathogens are shown in Table 1. These isolates comprised 88% of all tested isolates.
- Over 28% of *S. aureus* were oxacillin-resistant (MRSA). Tigecycline was highly active against *S. aureus* (MIC_{90}, 0.25 mg/L; 100% inhibited at ≤0.5 mg/L).
- At US-FDA published breakpoints, tigecycline exhibited complete inhibition of indicated species, except for a single strain of *E. cloacae* (MIC, 4 mg/L).
- Tigecycline was also very active against ß-haemolytic and viridans group streptococci ($MIC_{90,}$ 0.06 mg/L and ≤0.03 mg/L respectively; 100% susceptible). Despite high rates of penicillin-non-susceptibility in *S. pneumoniae*, all strains were inhibited by tigecycline at 0.06 mg/L.
- Modal tigecycline MIC values for *E. faecalis* and *E. faecium* were 0.12 mg/L; all species were inhibited at 0.12 mg/L, including one *vanA E. faecium* isolate.

Table 1. Activity of tigecycline against pathogens collected from Australia as part of the SENTRY Surveillance Program (2006).

	Number of isolates inhibited at each MIC (mg/L)								
Organism (n)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	%S[a]
S. aureus (465)	6	185	206	63	5				100
Oxacillin-susceptible (n=331)	5	147	148	30	1				100
Oxacillin-resistant (n=134)	1	38	58	33	4				100
E. coli (76)		15	42	17	1	1			100
S. pneumoniae (52)	51	1							100
Enterococcus spp. (51)	7	13	21	10					100
E. faecalis (n=40)		11	20	9					100
E. faecium (n=10)	7	1	1	1					100
Klebsiella spp. (40)			3	22	10	4	1		100
ß-haemolytic streptococci (47)[b]	37	9	1						100
viridans streptococci (21)	20	1							100
CoNS (24)[c]	1	5	9	7	2				100
Enterobacter spp. (22)				17	3	1		1	95.5
Moraxella catarrhalis (18)	7	8	3						-

a. US-FDA package insert criteria.
b. S. pyogenes (n=25); *S. agalactiae* (n=12); ß-haemolytic Group G *Streptococcus* (n=9); ß-haemolytic Group C *Streptococcus* (n=1).
c. CoNS = coagulase-negative staphylococci.

Table 2. Comparative tigecycline activity tested against selected Gram-positive isolates.

	MIC (mg/L)			
	MIC_{50}	MIC_{90}	Range	%susceptible
Oxacillin-resistant *S. aureus* (134)				
Tigecycline	0.12	0.25	≤0.03 - 0.5	100.0
Levofloxacin	4	>4	≤0.5 - >4	29.9
Tetracycline	≤2	>8	≤2 - >8	54.5
Linezolid	1	2	0.5 - 2	100.0
Vancomycin	1	2	0.5 - 2	100.0
E. faecalis (40)				
Tigecycline	0.12	0.25	0.06 – 0.25	100.0
Ampicillin	≤1	2	≤1 - 2	100.0
Linezolid	1	2	0.5 - 2	100.0
Vancomycin	1	2	1 - 4	100.0
E. faecium (10)				
Tigecycline	0.12	0.25	≤0.03 – 0.25	100.0
Ampicillin	>16	>16	2 - >16	10.0
Linezolid	1	2	1 - 2	100.0
Vancomycin	1	8	1 - >16	90.0
S. pneumoniae (52)				
Tigecycline	≤0.03	≤0.03	≤0.03 - 0.06	100.0
Penicillin	0.03	4	≤0.015 - 8	69.2
Erythromycin	≤0.25	>2	≤0.25 - >2	75.0
Levofloxacin	1	1	≤0.5 - 1	100.0

Table 3. Comparative tigecycline activity tested against *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

	MIC (mg/L)			
	MIC_{50}	MIC_{90}	Range	% susceptible
E. coli (76)				
Tigecycline	0.12	0.25	0.06 - 1	100.0
Tetracycline	≤2	>8	≤2 - >8	77.6
Ceftriaxone	≤0.25	≤0.25	≤0.25 - >32	97.4
Ceftazidime	≤1	≤1	≤1	100.0
Levofloxacin	≤0.5	≤0.5	≤0.5 - >4	96.1
Gentamicin	≤2	≤2	≤2 - >8	92.1
Imipenem	≤0.12	0.25	≤0.12 - 1	100.0
Klebsiella spp. (40)				
Tigecycline	0.25	1	0.12 - 2	100.0
Tetracycline	≤2	≤2	≤2 - >8	95.0
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 0.5	100.0
Ceftazidime	≤1	≤1	≤1 - 2	100.0
Levofloxacin	≤0.5	≤0.5	≤0.5 - >4	95.0
Gentamicin	≤2	≤2	≤2	100.0
Imipenem	0.25	0.5	≤0.12 - 1	100.0
Enterobacter spp. (22)				
Tigecycline	0.25	0.5	0.25 – 4	95.5
Tetracycline	≤2	>8	≤2 - >8	86.4
Ceftriaxone	≤0.25	>32	≤0.25 - >32	86.4
Ceftazidime	≤1	>16	≤1 - >16	81.8
Levofloxacin	≤0.5	≤0.5	≤0.5 - 2	100.0
Gentamicin	≤2	≤2	≤2 - >8	95.5
Imipenem	1	2	0.25 - 2	100.0

CONCLUSIONS

- Tigecycline was very active against almost all facultative human pathogens except *Pseudomonas aeruginosa* in Australia (2006). It retains activity against strains resistant to other drug classes, in particular, the prevalent multi-resistant *Staphylococcus aureus* (MLST-type 239), a well-documented hospital pathogen in many major hospitals in eastern and south central Australia.
- Resistance to tigecycline was not detected amongst Enterobacteriaceae or *Moraxella catarrhalis*. Other major resistances such as vancomycin resistance in enterococci, or carbapenemases, were uncommon in the monitored year. The rare strains collected with these resistances were susceptible to tigecycline.

SELECTED REFERENCES

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