Multicenter Evaluation of Tigecycline Activity in India: Report from the SENTRY Antimicrobial Surveillance Program (2006)

RN JONES, JM BELL, JD TURNIDGE, D MATHAI

JMI Laboratories, North Liberty, IA;
Women's and Children's Hospital, Adelaide, Australia;
Christian Medical College Hospital, Vellore, India

ICID 2008
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

ABSTRACT

Background: Tigecycline, the initial representative of the glycylcyclines, presents a therapy option for emerging multidrug-resistant (MDR) pathogens. India, a nation rarely monitored in global surveillance programs, appears in need of agents active against MDR isolates of Enterobacteriaceae (ESBLs), *Acinetobacters* (carbapenem-resistant) and Gram-positive cocci (MRSA, VRE). Numerous sites were sampled using reference susceptibility methods.

Methods: Eleven sites forwarded 1,714 strains to a regional monitor (WCH, Adelaide, Australia) that susceptibility tested 27 antimicrobials by CLSI methods (M7-A7, 2006). Identifications were confirmed and interpretive/screening criteria were also by CLSI guidelines (M100-S18, 2008), except for tigecycline where United States - Food and Drug Administration breakpoints were applied. Major pathogens were: *S. aureus* (250), coagulase-negative staphylococci (CoNS; 228), enterococci (93), *Enterobacter* spp. (76), *E. coli* (217), *K. pneumoniae* (268), *Salmonella* spp. (55) and *Acinetobacter* spp. (108).

Results: Tigecycline was active against 98-100% of indicated/tabulated species, lowest for *Acinetobacter* spp. *S. aureus* tigecycline MIC_{90} values were not influenced by oxacillin susceptibility patterns (0.25 mg/L; 100% S). Increased resistance patterns noted were: tetracycline-resistant (4-100%; average 53%), AmpC, ESBL- and fluoroquinolone resistance in Enterobacteriaceae (8-70, 14-78, 1-91%, respectively), VRE (1%), MRSA (36%) and *Acinetobacters* carbapenem-resistant (38%). *S. typhi* and *S. paratyphi* were common (tigecycline MIC_{90}, 0.5 mg/L), and 84% were nalidixic acid-resistant. Carbapenem resistance in Enterobacteriaceae (1-7%) was consistent with harbouring metallo-ß-lactamases; confirmed by PCR testing.

Organism (no. tested)	Cum. % inhibited at MIC (mg/L): ≤0.06	0.12	0.25	0.5	1	2	4	% S[a]
S. aureus (250)	9	58	98	100				100.0
Enterococci (93)	12	70	100					100.0
E. coli (217)	1	23	76	>99	100			100.0
Enterobacters (76)	0	1	16	79	93	100		100.0
K. pneumoniae (268)	0	0	24	74	96	99	>99	98.5
Salmonella spp. (55)	0	15	56	98	100			100.0
Acinetobacters (108)	2	21	40	75	95	98	>99	98.1

a. US-FDA and Jones et al. (2007) criteria.

Conclusions: Although MDR rates across Gram-positive and -negative species (particularly among enteric bacilli and *Acinetobacters*) was high in India, tigecycline remained active (MIC_{90}, 1 mg/L overall) against these MDR strains. Tigecycline exhibited promising spectrum/potency exceeding currently available agents against sampled isolates from India.

INTRODUCTION

Tigecycline is a semisynthetic glycylcycline derived from minocycline that induces its bacteriostatic effect by binding to a single 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 of drug and protection of ribosomes. It appears to resist these mechanisms as a result of steric hindrance produced by the large substituent at position 9. Thus, tigecycline possesses documented activity against tetracycline-resistant Gram-positive and -negative pathogens refractory to treatment by efflux and/or ribosomal protection mechanisms. In addition, this antimicrobial agent has demonstrated excellent activity against multidrug-resistant (MDR) pathogens, including oxacillin-resistant (MRSA) and glycopeptide-intermediate *Staphylococcus aureus* (VISA), vancomycin-resistant enterococci (VRE), penicillin-resistant *Streptococcus pneumoniae*, extended-spectrum ß-lactamase (ESBL)-producing Enterobacteriaceae and some non-fermentative Gram-negative bacilli, such as *Acinetobacter* spp. and *Stenotrophomonas maltophilia*.

The objective of this study was to evaluate the potency and spectrum of tigecycline activity tested against bacterial pathogens isolated during 2006 from medical centers located in India.

MATERIALS AND METHODS

Bacterial isolates. A total of 1,714 bacterial isolates collected during 2006 in 11 medical centers located in India 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, formerly NCCLS). 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.

SELECTED REFERENCES

1. Clinical and Laboratory Standards Institute. (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition.* Wayne, PA: CLSI.
2. Clinical and Laboratory Standards Institute. (2008). *M100-S18, Performance standards for antimicrobial susceptibility testing, 18th informational supplement.* Wayne, PA: CLSI.
3. Ko KS, Song JH, Lee MY, Park S, Kwon KT, Heo ST, Ryu SY, Oh WS, Peck KR, Lee NY (2006). Antimicrobial activity of tigecycline against recent isolates of respiratory pathogens from Asian countries. *Diagn Microbiol Infect Dis* 55: 337-341.
4. Reinert RR, Low DE, Rossi F, Zhang X, Wattal C, Dowzicky MJ (2007). Antimicrobial susceptibility among organisms from the Asia/Pacific Rim, Europe and Latin and North America collected as part of TEST and the in vitro activity of tigecycline. *J Antimicrob Chemother* 60: 1018-1029.
5. Sader HS, Jones RN, Dowzicky MJ, Fritsche TR (2005). Antimicrobial activity of tigecycline tested against nosocomial bacterial pathogens from patients hospitalized in the intensive care unit. *Diagn Microbiol Infect Dis* 52: 203-208.

RESULTS

- Tigecycline showed pronounced activity against Gram-positive clinical isolates, with 100.0% susceptibility for *S. aureus* and *Enterococcus* spp. (Table 1).
- Tigecycline potency against oxacillin-resistant *S. aureus* (MIC_{90} 0.25 mg/L) was the same as the potency for oxacillin-susceptible strains.
- Among Gram-negative isolates, tigecycline demonstrated 100.0% activity against *E. coli*, and various species of *Enterobacter* and *Salmonella* (Table 1).
- The activity of tigecycline against *K. pneumoniae* and *Acinetobacter* spp. was slightly lower at 98.5 and 98.1%, respectively, and only 0.7 to 0.9% of strains were categorized as resistant (Table 1).
- Tigecycline was very active against tetracycline-resistant strains that were observed in 4.0 to 100.0% (average 53.0%) of isolates.
- Overall, tigecycline remained active (MIC_{90}, 1 mg/L) against isolates harbouring important resistance mechanisms including: AmpC, ESBL-producing strains, fluoroquinolone resistance in Enterobacteriaceae, VRE, MRSA and carbapenem-resistant *Acinetobacter* spp.
- Among *Salmonella* spp. isolates, 54.5% were *S. typhi* and 38.2% were *S. paratyphi*. A total of 84.2% were nalidixic acid-resistant (1.8% resistant to ciprofloxacin); tigecycline (MIC_{90}, 0.5 mg/L) showed good activity and potency against these isolates.
- Carbapenem resistance in Enterobacteriaceae was low and most resistant isolates were carbapenemase-producers.

Table 1. In vitro activity of tigecycline in comparison to selected antimicrobial agents tested against 1,714 clinical isolates from India collected in 2006 as part of the SENTRY Antimicrobial Surveillance Program.

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
S. aureus				
Tigecycline[b]	0.12	0.25	0.06 – 0.5	100.0 / -
Oxacillin	0.5	>2	≤0.25 – >2	64.0 / 36.0
Erythromycin	0.5	>2	≤0.25 – >2	54.0 / 44.8
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	95.2 / 4.8
Vancomycin	1	1	0.5 – 2	100.0 / 0.0
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0
Enterococcus spp.				
Tigecycline[b]	0.12	0.25	≤0.03 – 0.25	100.0 / -
Ampicillin	≤1	>16	≤1 – >16	79.6 / 20.4
Erythromycin	>2	>2	≤0.25 – >2	20.4 / 57.0
Quinupristin/dalfopristin	>2	>2	0.5 – >2	21.5 / 68.8
Vancomycin	1	2	0.5 – >16	98.9 / 1.1
Teicoplanin	≤2	≤2	≤2 – >16	98.9 / 1.1
Linezolid	2	2	1 – 2	100.0 / 0.0
Gentamicin (HL)	≤500	>1000	≤500 – >1000	61.3 / 38.7
Streptomycin (HL)	≤1000	>2000	≤1000 – >2000	69.9 / 30.1
Ciprofloxacin	>4	>4	0.25 – >4	39.8 / 53.8
Tetracycline	>8	>8	≤2 – >8	38.7 / 61.3
E. coli				
Tigecycline[b]	0.25	0.5	0.06 – 1	100.0 / 0.0
Piperacillin/tazobactam	8	64	≤0.5 – >64	79.3 / 9.7
Cefepime	>16	>16	≤0.12 – >16	20.7 / 65.9
Ceftriaxone	>32	>32	≤0.25 – >32	16.6 / 82.9
Ceftazidime	16	>16	≤1 – >16	27.2 / 38.7
Gentamicin	>8	>8	≤2 – >8	37.3 / 61.8
Amikacin	≤4	16	≤4 – >32	95.9 / 3.2
Ciprofloxacin	>4	>4	≤0.03 – >4	8.8 / 90.3
Imipenem	0.25	0.25	≤0.12 – 1	100.0 / 0.0
Polymyxin B	≤0.5	≤0.5	≤0.5 – 1	100.0 / 0.0
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	34.1 / 65.9
Tetracycline	>8	>8	≤2 – >8	22.6 / 77.0
Enterobacter spp.				
Tigecycline[b]	0.5	1	0.12 – 2	100.0 / 0.0
Piperacillin/tazobactam	16	>64	1 – >64	60.5 / 25.0
Cefepime	>16	>16	≤0.12 – >16	34.2 / 59.2
Ceftriaxone	>32	>32	≤0.25 – >32	23.7 / 75.0
Ceftazidime	>16	>16	≤1 – >16	30.3 / 51.3
Gentamicin	>8	>8	≤2 – >8	32.9 / 67.1
Amikacin	≤4	>32	≤4 – >32	78.9 / 15.8
Ciprofloxacin	2	>4	≤0.03 – >4	42.1 / 46.1
Imipenem	0.5	1	≤0.12 – >8	98.7 / 1.3
Polymyxin B	≤0.5	4	≤0.5 – >4	89.5 / 10.5
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	43.4 / 56.6
Tetracycline	>8	>8	≤2 – >8	47.4 / 51.3
K. pneumoniae				
Tigecycline[b]	0.5	1	0.25 – >4	98.5 / 0.7
Piperacillin/tazobactam	16	>64	1 – >64	52.2 / 23.9
Cefepime	>16	>16	≤0.12 – >16	29.5 / 52.2
Ceftriaxone	>32	>32	≤0.25 – >32	16.4 / 80.6
Ceftazidime	>16	>16	≤1 – >16	23.9 / 61.6
Gentamicin	>8	>8	≤2 – >8	26.1 / 73.5
Amikacin	≤4	>32	≤4 – >32	83.2 / 12.7
Ciprofloxacin	>4	>4	≤0.03 – >4	27.2 / 58.6
Imipenem	0.25	0.5	≤0.12 – 4	100.0 / 0.0
Polymyxin B	≤0.5	≤0.5	≤0.5 – >4	98.9 / 1.1
Trimethoprim/sulfamethoxazole	>2	>2	≤0.5 – >2	32.5 / 67.5
Tetracycline	>8	>8	≤2 – >8	46.3 / 52.6
Salmonella spp.				
Tigecycline[b]	0.25	0.5	0.12 – 1	100.0 / 0.0
Piperacillin/tazobactam	2	4	1 – 4	100.0 / 0.0
Ampicillin	2	2	≤1 – 4	100.0 / 0.0
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / 0.0
Gentamicin	≤2	≤2	≤2 – 8	98.2 / 0.0
Amikacin	≤4	≤4	≤4	100.0 / 0.0
Ciprofloxacin	0.5	0.5	≤0.03 – >4	98.2 / 1.8
Levofloxacin	≤0.5	1	≤0.5 – >4	98.2 / 1.8
Imipenem	0.25	0.25	≤0.12 – 0.5	100.0 / 0.0
Polymyxin B	≤0.5	≤0.5	≤0.5 – 2	100.0 / 0.0
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	96.4 / 3.6
Acinetobacter spp.				
Tigecycline	0.5	1	≤0.03 – >4	98.1/0.9[c]
Ampicillin/sulbactam	>16	>16	≤2 – >16	41.9 / 50.4
Cefepime	>16	>16	0.25 – >16	33.3 / 55.6
Ceftriaxone	>32	>32	2 – >32	21.4 / 67.5
Ceftazidime	>16	>16	≤1 – >16	31.6 / 67.5
Gentamicin	>8	>8	≤2 – >8	31.6 / 67.5
Amikacin	>32	>32	≤4 – >32	32.5 / 66.7
Ciprofloxacin	>4	>4	0.06 – >4	29.1 / 70.9
Imipenem	2	>8	≤0.12 – >8	61.5 / 36.8
Levofloxacin	>4	>4	≤0.5 – >4	33.3 / 55.6
Polymyxin B	≤0.5	1	≤0.5 – 1	100.0 / 0.0
Tetracycline	8	>8	≤2 – >8	46.2 / 39.3

a. Criteria as published by the CLSI [2008].
b. US-FDA breakpoints were applied [Tygacil Product Insert, 2005].
c. Breakpoints for Enterobacteriaceae were applied for comparison purposes only.

CONCLUSIONS

- Antimicrobial activity of tigecycline was largely unaffected by mechanisms that most commonly occur in Gram-positive and Gram-negative organisms in India.
- This novel compound could be a valuable therapeutic option for the treatment of infections caused by these troublesome pathogens in this nation.

ACKNOWLEDGEMENT

This study was suppported by an educational/research grant from Wyeth Pharmaceuticals.