Activity of Tigecycline When Tested Against Gram-positive Pathogens in North American Hospitals (2006)

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ABSTRACT

Background:
A new class of glycylcyclines represented by tigecycline has broad-spectrum activity against contemporary pathogens including multidrug-resistant (MDR) isolates of MRSA, VRE and *S. pneumoniae* (SPN). Tigecycline was approved by the US-FDA for serious infections such as cSSSI and intra-abdominal sepsis. Tigecycline activity for NA GP spp. was assessed across numerous participating institutions.

Methods: Consecutive patient isolates were collected in the USA and Canada (2006; >30 sites). The organisms were obtained from SENTRY Program objectives covering bacteremia (3,829), pneumonia (933), CA-RTI (1,071) and other infections (5,895). Susceptibility (S) testing was performed by CLSI broth microdilution methods. The most commonly isolated pathogens were *S. aureus* (SA; 5,139), enterococci (ENT; 1,394), SPN (1,115), CoNS (919), ß-hemolytic (BST; 497) and vir. gr. streptococci (VGS; 240).

Results: Tigecycline was very potent against contemporary Gram-positive organisms with MIC_{90} results ranging from ≤0.03 (streptococci) to 0.25 mg/L. Only 8 (0.09%) isolates were one doubling dilution higher than the US-FDA S breakpoint (see Table). MRSA (2,773; 54.0%) had tigecycline $MIC_{950/90}$ results (0.12/0.25 mg/L that were identical to that of all SA.

	Cum. % inhibited at tigecycline MIC (mg/L):					
Organism (no. tested)	≤0.06	0.12	0.25	0.5	1	%S
SA (5,139)	29.5	82.4	99.1	>99.9[a]	100.0[b]	99.98
CoNS (919)	33.7	24.6	98.4	100.0[a]	-	100.00
ENT (1,394)	50.5	86.3	99.5[a]	100.0[c]	-	99.50
SPN (1,115)	99.8	100.0	-[a]	-	-	100.00
VGS (240)	92.9	98.8	100.0[a]	-	-	100.00
BST (497)	98.2	100.0	-[a]	-	-	100.00

a. US-FDA S breakpoints.
b. One strain (0.02%).
c. 7 strains (0.50%).

Conclusions:
Tigecycline demonstrated a remarkable spectrum and potency against Gram-positive pathogens from NA with >99.9% of isolates being declared S using US-FDA approved breakpoints. This glycylcycline is a welcome addition to the formularies in this geographic region.

INTRODUCTION

Tigecycline is the first glycylcycline to be marketed and represents an example of a new class of antimicrobials that addresses several critical needs. Since the start of clinical testing (1998), several tigecycline clinical trials have been reported involving patients with complicated skin and skin structure infections (cSSSI) and in patients with intra-abdominal infections (IAI); the agent was subsequently approved (June 2005) by the US-FDA for these indications. Tigecycline has demonstrated potent activity against a broad range of commonly occurring species, including many resistant organisms such as penicillin-resistant *S. pneumoniae*, oxacillin-resistant *S. aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum ß-lactamase (ESBL)-producing strains of Enterobacteriaceae. The agent was also active against *Haemophilus influenzae*, *Moraxella catarrhalis*, pathogenic *Neisseriae* and many other Gram-negative species, including some nonfermentative Gram-negative bacilli.

Documentation of the increasing rates of antimicrobial resistances, including multidrug resistance (MDR), is commonplace and being observed in both Gram-positive and Gram-negative pathogens. A variety of factors are responsible for this phenomenon that include microbiologic-related changes (selective pressures and genetic mechanisms that aid in resistance dissemination) and societal/healthcare-related changes (changing population demographics, lack of formulary controls and prescription discipline, lack of resources for appropriate infection control practices and a declining public health infrastructure). Unfortunately, the pharmaceutical development pipeline for new antimicrobial agents has become concurrently limited at a time when they are needed most. In this report, we document the activity of tigecycline tested against a large collection of Gram-positive pathogens isolated in North American hospitals (2006).

MATERIALS AND METHODS

Consecutive patient isolates were collected in the USA and Canada (2006; >30 medical centers). The organisms were obtained from SENTRY Antimicrobial Surveillance Program protocol objectives covering bacteremia (3,829), pneumonia (933), community-acquired respiratory tract infections (CA-RTI; 1,071) and other infections (5,895).

Susceptibility testing was performed by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods and interpreted by CLSI M100-S17 (2007) for all comparison agents and by US-FDA package insert criteria for tigecycline (2005). The most commonly isolated pathogens were *S. aureus* (SA; 5,139), enterococci (ENT; 1,394), *S. pneumoniae* (1,115), coagulase-negative staphylococci (CoNS; 919), ß-haemolytic streptococci (497) and viridans group streptococci (240). Concurrent quality control (QC) was performed with all results within published QC ranges (see CLSI M100-S17, 2007).

RESULTS

- A total of 9,684 Gram-positive pathogens were screened for tigecycline susceptibility with strains derived from more than 30 medical centers in North America (Table 1).
- Tigecycline was very active against *S. aureus* (MIC_{90}, 0.25 mg/L) and CoNS (MIC_{90}, 0.25 mg/L) strains including MRSA (2,773 strains; MIC_{90}, 0.25 mg/L). Only one tigecycline-non-susceptible (MIC, 1 mg/L) strain was detected (0.02%). The MRSA rate was 54.0%.
- All but seven (0.5%) enterococcal isolates were susceptible to tigecycline (MIC_{90}, 0.25 mg/L) including the 26.6% of strains that were VRE (2.4% were linezolid-resistant).
- Streptococci were very susceptible to tigecycline with MIC_{90} results ranging from ≤0.03 mg/L (ß-haemolytic and *S. pneumoniae*) to 0.06 mg/L (viridans group streptococci). Tigecycline inhibited all streptococci at ≤0.25 mg/L (Table 1).

CONCLUSIONS

- Tigecycline demonstrated remarkable activity against commonly isolated North American Gram-positive pathogens in 2006 (MIC_{90}, range, ≤0.03 to 0.25 mg/L).
- Only eight (0.08%) isolates were non-susceptible to tigecycline, and each of these strains were only one doubling dilution above the US-FDA approved breakpoint for susceptibility.
- Tigecycline appears to be an excellent alternative in North America to treat serious infections caused by Gram-positive species found to be refractory to other antimicrobial classes.

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Table 1. Comparative activity of tigecycline tested against nearly 10,000 Gram-positive pathogens isolated from patients in North America (2006).

		Cumulative % inhibited at MIC (mg/L):								MIC (mg/L)		% by Category:[a]	
Organism (no. tested)	Antimicrobial	≤0.06	0.12	0.25	0.5	1	2	4	8	50%	90%	Susceptible	Resistant
S. aureus (5,139)	Tigecycline	30	82	>99	>99	100	-	-	-	0.12	0.25	>99.9	-[b]
	Oxacillin	-	-	28	44	46	46	-	-	>2	>2	46.0	54.0
MRSA (2,773)	Tigecycline	28	79	99	>99	100	-	-	-	0.12	0.25	>99.9	-
	Linezolid	0	0	<1	1	47	>99	>99	>99	2	2	>99.9	-
	Vancomycin	0	0	<1	11	96	>99	100	-	1	1	>99.9	0.0
CoNS (919)	Tigecycline	34	75	98	100	-	-	-	-	0.12	0.25	100.0	-
	Oxacillin	-	-	24	28	34	45	-	-	>2	>2	24.0	76.0
	Linezolid	<1	<1	2	39	98	99	99	99	1	1	98.9	-
	Vancomycin	0	0	1	10	66	100	-	-	1	2	100.0	0.0
Enterococci (1,394)	Tigecycline	51	86	>99	100	-	-	-	-	0.06	0.25	100.0	-
	Ampicillin	-	-	-	-	56	68	68	69	≤1	>16	68.6	31.4
	Vancomycin	0	0	<1	7	53	71	73	73	1	>16	72.7	26.6
VRE (380)	Tigecycline	71	96	>99	100	-	-	-	-	0.06	0.12	100.0	-
	Linezolid	0	0	0	1	68	96	98	>99	1	2	96.6	2.4
S. pneumoniae (1,115)	Tigecycline	>99	100	-	-	-	-	-	-	≤0.03	≤0.03	100.0	-
	Penicillin	66	73	79	81	85	91	>99	-	≤0.03	2	66.2	15.5
	Erythromycin	-	-	67	67	68	69	-	-	≤0.25	>2	66.5	32.9
	Levofloxacin	-	-	-	22	98	>99	>99	-	1	1	99.3	0.4
	Vancomycin	-	-	-	-	100	-	-	-	≤1	≤1	100.0	-
viridans group streptococci (240)	Tigecycline	93	99	100	-	-	-	-	-	≤0.03	0.06	100.0	-
	Penicillin	57	73	81	89	95	97	99	100	0.06	1	73.3	3.3
	Erythromycin	-	-	46	48	55	70	-	-	1	>2	45.8	52.5
	Levofloxacin	-	-	-	39	89	95	96	-	1	2	95.0	4.2
	Vancomycin	-	<1	17	91	100	-	-	-	0.5	0.5	100.0	-
ß-haemolytic streptococci (497)	Tigecycline	98	100	-	-	-	-	-	-	≤0.03	≤0.03	100.0	-
	Penicillin	98	100	-	-	-	-	-	-	≤0.015	0.06	100.0	-
	Erythromycin	-	-	72	72	74	80	-	-	≤0.25	>2	71.6	28.0
	Levofloxacin	-	-	-	89	98	>99	>99	-	≤0.5	1	99.4	0.6
	Vancomycin	-	<1	47	98	100	-	-	-	0.5	0.5	100.0	-

a. All tests interpreted by CLSI criteria except tigecycline where US-FDA package insert breakpoints were applied (2005).
b. No criteria for this category have been proposed.

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