

In Vitro Activity of Tigecycline Against Pathogens Isolated from Most Common Body Sites - Eastern European Data - T.E.S.T. Program 2006

#P1-002

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REVISED ABSTRACT

Background: Tigecycline (TIG), a new glycolcycline, has been shown to have potent broad spectrum activity against most commonly encountered species responsible for community and hospital acquired infections. The T.E.S.T. program determined the *in vitro* activity of TIG and 10 comparators against respective gram positive/negative species. For the overall T.E.S.T. program isolates were collected from 205 hospital sites in 30 countries from 2004 to 2006. **Methods:** In this survey, clinically significant isolates from East European testing sites (Poland, Hungary, Greece, and Latvia) were analyzed. The isolates were identified to the species level at the participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI (formerly NCCLS) guidelines. **Results:** TIG activity against pathogens from selected body sites are shown in the table below*:

	Blood			Respiratory			Urinary tract		
	n	%S ^a	MIC ₉₀ ^a	n	%S ^a	MIC ₉₀ ^a	n	%S ^a	MIC ₉₀ ^a
EckpKo	26	100	1	40	98	0.5	77	99	0.5
<i>Enterobacter</i> spp.	11	100	1	27	96	2	14	93	1
<i>Acinetobacter</i> spp.	9	na	-	40	na	1	6	na	-
<i>S. aureus</i>	17	100	0.12	25	100	0.12	7	100	-
<i>Enterococcus</i> spp.	12	100	0.12	5	100	-	20	100	0.12
<i>S. pneumoniae</i>	17	na	1	37	na	1	0	0	-
<i>H. influenzae</i>	1	na	-	56	na	0.25	0	-	-

* na = breakpoints not available
* No MIC₉₀ calculated if n<10; %S may not be statistically significant when n's are small.

Conclusion: Tigecycline showed excellent inhibitory activity against all groups of pathogens regardless of isolation site. Tigecycline MIC₉₀ of ≤ 1 mcg/ml against Gram positive pathogens (including resistant phenotypes) and MIC₉₀ of ≤ 2 mcg/ml against *Enterobacteriaceae* and *Acinetobacter* spp. validate the potent inhibitory activity of TIG against Eastern European community/hospital pathogens.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycolcyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that tigecycline and other glycolcyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restore activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3]. Furthermore, resistance to tigecycline is difficult to produce even in the laboratory.

Previous studies have demonstrated excellent *in vitro* activity for tigecycline against clinical and laboratory strains of gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90th percentile inhibited at or below 2 mcg/ml, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the *in vitro* activity of tigecycline against significant numbers of clinical pathogens collected in Eastern European laboratories. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) program with isolates collected from 205 hospital sites in 30 countries from 2004 to 2006.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested from 2004 to 2006 from 5 study centers in Eastern Europe. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database, were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age, or gender. All sites identified each study isolate utilizing local laboratory criteria.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [7]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., West Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.5-32, gram-negative panel, and 0.06-16, gram-positive panel); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [8] and the recent US Food and Drug Administration package insert for tigecycline [9], where applicable.
- Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftaxone were >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2006) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2006) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: ceftaxime (30-mcg), ceftaxime/clavulanic acid (30/10-mcg), ceftazidime (30-mcg), and ceftazidime/clavulanic acid (30/10-mcg). Antimicrobial disks were manufactured by Oxoid, Inc. (Ogdensburg, NY, USA). Mueller-Hinton agar used in testing was manufactured by Remel, Inc. (Lenexa, KS, USA). An organism was interpreted as containing an ESBL if there was an increase of >5 mm in the inhibition zone of the combination disk when compared to that of the cephalosporin alone. *K. pneumoniae* ATCC 700793 was used to QC the ESBL confirmation test.
- Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2006) guidelines [8].

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ACKNOWLEDGEMENTS

We gratefully acknowledge the contributions of the investigators, laboratory personnel, and all members of the Tigecycline Evaluation Study Trials program group. This study was sponsored by a grant from Wyeth Pharmaceuticals.

RESULTS

The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and comparative agents against 92 blood culture isolates

Organism Name	Drug	%SUS ^a	%INT	%RES	MIC (µg/ml)		MIC range (µg/ml)		
					MIC ₅₀	MIC ₉₀	Low	High	
<i>E. coli</i> (n=10)	Tigecycline	100	0	0	0.12	0.25	0.06	0.5	
	Amikacin	100	0	0	2	4	1	4	
	AmoxClav	80	10	10	8	16	2	32	
	Ampicillin	40	0	60	32	>32	1	>32	
	Cefepime	100	0	0	≤0.5	≤0.5	≤0.5	≤0.5	
	Ceftazidime	100	0	0	≤8	≤8	≤8	≤8	
	Ceftriaxone	100	0	0	≤0.06	0.12	≤0.06	0.12	
	Imipenem	100	0	0	0.25	0.5	0.25	0.5	
	Levofloxacin	90	10	0	0.015	4	≤0.008	4	
	Minocycline	100	0	0	≤0.5	4	≤0.5	4	
	PipTazo	100	0	0	1	1	0.5	2	
	<i>Klebsiella</i> spp. ^b (n=16)	Tigecycline	100	0	0	0.5	2	0.12	2
Amikacin		93.8	0	6.3	4	16	1	>64	
AmoxClav		81.3	6.3	12.5	4	>32	1	>32	
Ampicillin		0	6.3	93.8	>32	>32	16	>32	
Cefepime		81.3	6.3	12.5	≤0.5	32	≤0.5	>32	
Ceftazidime		62.5	0	37.5	≤8	>32	≤8	>32	
Ceftriaxone		68.8	6.3	25	≤0.06	>64	≤0.06	>64	
Imipenem		100	0	0	0.25	0.5	0.25	2	
Levofloxacin		43.8	25	31.3	4	>8	0.03	>8	
Minocycline		81.3	18.8	0	2	8	≤0.5	8	
PipTazo		81.3	0	18.8	2	>128	0.5	>128	
<i>Enterobacter</i> spp. (n=11)		Tigecycline	100	0	0	0.5	1	0.12	1
	Amikacin	100	0	0	1	2	≤0.5	16	
	AmoxClav	0	18.2	81.8	>32	>32	16	>32	
	Ampicillin	0	18.2	81.8	>32	>32	16	>32	
	Cefepime	90.9	0	9.1	≤0.5	4	≤0.5	32	
	Ceftazidime	63.6	9.1	27.3	≤8	>32	≤8	>32	
	Ceftriaxone	72.7	9.1	18.2	0.5	64	≤0.06	>64	
	Imipenem	100	0	0	0.5	0.5	0.25	2	
	Levofloxacin	100	0	0	0.06	0.12	0.03	0.5	
	Minocycline	72.7	18.2	9.1	4	8	2	16	
	PipTazo	63.6	18.2	18.2	2	>128	1	>128	
	<i>Acinetobacter</i> spp. ^c (n=9)	Tigecycline	na	na	na	-	-	0.06	1
Amikacin		22.2	11.1	66.7	-	-	1	>64	
AmoxClav		na	na	na	-	-	0.5	>32	
Ampicillin		na	na	na	-	-	1	>32	
Cefepime		55.6	22.2	22.2	-	-	2	>32	
Ceftazidime		44.4	22.2	33.3	-	-	≤8	>32	
Ceftriaxone		33.3	11.1	55.6	-	-	1	>64	
Imipenem		77.8	11.1	11.1	-	-	0.25	>16	
Levofloxacin		44.4	0	55.6	-	-	0.06	>8	
Minocycline		100	0	0	-	-	≤0.5	4	
PipTazo		33.3	11.1	55.6	-	-	≤0.06	>128	
<i>S. aureus</i> ^d (n=17)		Tigecycline	100	0	0	0.12	0.12	0.06	0.25
	AmoxClav	76.5	0	23.5	1	>8	0.12	>8	
	Ampicillin	5.9	0	94.1	8	>16	≤0.06	>16	
	Ceftriaxone	76.5	5.9	17.6	4	>64	1	>64	
	Imipenem	82.4	0	17.6	≤0.12	>16	≤0.12	>16	
	Levofloxacin	76.5	0	23.5	0.12	4	≤0.06	32	
	Linezolid	100	0	0	2	2	1	2	
	Minocycline	100	0	0	≤0.25	4	≤0.25	4	
	Penicillin	5.9	0	94.1	>8	>8	≤0.06	>8	
	PipTazo	76.5	0	23.5	1	>16	≤0.25	>16	
	Vancomycin	100	0	0	0.5	2	0.5	4	
	<i>Enterococcus</i> spp. (n=12)	Tigecycline	100	0	0	0.12	0.12	0.03	0.12
Amikacin		75	0	25	1	>16	0.5	>16	
Levofloxacin		75	0	25	1	32	0.5	32	
Linezolid		100	0	0	1	2	≤0.5	2	
Minocycline		83.3	16.7	0	4	8	≤0.25	8	
Penicillin		75	0	25	2	>8	1	>8	
Vancomycin		100	0	0	1	0.5	2	2	
<i>S. pneumoniae</i> ^e (n=17)		Tigecycline	na	na	na	0.25	1	0.015	1
		AmoxClav	100	0	0	≤0.03	0.12	≤0.03	1
		Ceftriaxone	100	0	0	≤0.03	0.5	≤0.03	0.5
		Imipenem	94.1	5.9	0	≤0.12	≤0.12	≤0.12	0.25
		Levofloxacin	100	0	0	0.5	1	0.25	1
	Linezolid	100	0	0	≤0.5	≤0.5	≤0.5	1	
	Penicillin	82.2	5.9	5.9	≤0.06	0.12	≤0.06	2	
	Vancomycin	100	0	0	0.25	0.5	≤0.12	0.5	

Table 2. In vitro activity of tigecycline and comparative agents against 230 respiratory isolates

Organism Name	Drug	%SUS ^a	%INT	%RES	MIC (µg/ml)		MIC range (µg/ml)	
					MIC ₅₀	MIC ₉₀	Low	High
<i>E. coli</i> (n=15)	Tigecycline	100	0	0	0.12	0.25	0.06	0.5
	Amikacin	100	0	0	4	8	2	8
	AmoxClav	53.3	23.3	8	32	2	8	>32
	Ampicillin	8.4	0	84.4	>32	>32	1	>32
	Cefepime	84.4	0	15.6	≤0.5	≤0.5	≤0.5	>32
	Ceftazidime	84.4	0	15.6	≤8	≤8	≤8	>32
	Ceftriaxone	84.4	0	15.6	≤0.06	0.12	≤0.06	>32
	Imipenem	100	0	0	0.25	0.5	0.25	0.5
	Levofloxacin	85.3	23.3	11.1	1	>8	≤0.06	>8
	Minocycline	85.3	23.3	11.1	1	16	≤0.5	16
	PipTazo	84.4	15.6	0	1	32	0.5	64
	<i>Acinetobacter</i> spp. (n=10)	Tigecycline	84.4	0	0	0.25	1	0.12
Amikacin		84.4	0	0	1	2	1	>64
AmoxClav		84.4	0	0	1	2	0.5	>32
Ampicillin		8.4	0	84.4	>32	>32	1	>32
Cefepime		84.4	0	0	≤0.5	≤0.5	≤0.5	>32
Ceftazidime		84.4	0	0	≤8	≤8	≤8	>32
Ceftriaxone		84.4	0	0	≤0.06	0.12	≤0.06	>32
Imipenem		100	0	0	0.25	0.5	0.25	0.5
Levofloxacin		84.4	0	0	0.12	0.12	0.06	>8
Minocycline		84.4	0	0	0.5	4	0.5	16
PipTazo		84.4	0	0	1	1	0.5	16
All ESBL producers ^f (n=23)		Tigecycline	85.3	0	0	0.12	0.12	0.03
	Amikacin	85.3	0	0	1	2	1	>64
	AmoxClav	26.3	26.3	0	8	16	2	>32
	Ampicillin	0	0	100	>32	>32	1	>32
	Cefepime	12.5	0	87.5	8	16	2	>32
	Ceftazidime	85.3	0	14.7	≤8	≤8	≤8	>32
	Ceftriaxone	85.3	0	14.7	≤0.06	0.12	≤0.06	>32
	Imipenem	100	0	0	0.25	0.5	0.25	0.5
	Levofloxacin	85.3	0	14.7	0.12	0.12	0.06	>8
	Minocycline	85.3	0	14.7	0.5	4	0.5	16
	PipTazo	85.3	0	14.7	1	1	0.5	16
	<i>Enterobacter</i> spp. (n=23)	Tigecycline	82.6	0	0	0.12	0.12	0.03
Amikacin		82.6	0	0	1	2	1	>64
AmoxClav		26.3	26.3	0	8	16	2	>32
Ampicillin		0	0	100	>32	>32	1	>32
Cefepime		12.5	0	87.5	8	16	2	>32
Ceftazidime		85.3	0	14.7	≤8	≤8	≤8	>32
Ceftriaxone		85.3	0	14.7	≤0.06	0.12	≤0.06	>32
Imipenem		100	0	0	0.25	0.5	0.25	0.5
Levofloxacin		85.3	0	14.7	0.12	0.12	0.06	>8
Minocycline		85.3	0	14.7	0.5	4	0.5	