Efficacy of Tigecycline Against Worldwide Levofloxacin-Resistant Pathogens

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REVISED ABSTRACT

Objectives: Tigecycline (TIG) is the first member of the glycylcycline class of anti-infectives to be marketed, exhibiting a broad spectrum of antibacterial activity against many commonly isolated pathogens. This study evaluates the in vitro activity of TIG versus levofloxacin (LEV)-resistant strains in a large set of isolates collected globally from 2004-2008. **Methods**: 14,690 LEV-resistant isolates were identified to the species level at participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results**: Percentages of LEV-resistant isolates susceptible to TIG are summarized in the following table:

Organism (n)	No. LEV-Resistant (%)	% Susceptible to TIG
E. coli (13,780)	3596 (26.1)	100
Klebsiella spp. (13,360)	1697(12.7)	88.9
ESBL+ (2,552)	1619(63.4)	94.6
Enterobacter spp. (12,247)	1175(9.6)	80.1
Serratia spp. (5,059)	182(3.6)	83.5
S. aureus MR (5,894)	3972(67.4)	99.8
S. aureus MS (7,342)	182(2.5)	100
Enterococcus spp., all (8,107)	3886(47.9)	99.8

Conclusions: LEV resistance varied in this study from 2.5% in methicillin-sensitive *S. aureus* to 67.4 % in methicillin-resistant *S. aureus*. When resistance to LEV was seen, however, TIG retained activity in the vast majority of such strains. TIG's broad spectrum of activity, including strains resistant to other drugs, makes it a valuable tool for treating serious infections caused by bacteria that may be refractory to treatment with commonly used antimicrobials such as LEV.

BACKGROUND

Tigecycline is a novel antimicrobial with expanded broad-spectrum activity from a new class of compounds, the glycylcyclines. Tigecycline inhibits protein synthesis by binding to the 30S ribosomal subunit. Although it is perceived to be bacteriostatic, its anti-bacterial activity is significant and has shown some bactericidal activity against key targeted pathogens [1,2]. Tigecycline has demonstrated significant broad-spectrum activity against aerobic and anaerobic gram-positive and gram-negative microorganisms [2-4].

Tigecycline resistance is very infrequent and is also difficult to induce in the laboratory [5, 6] with a selection frequency observed at less than 10^{-9} [3, 5, 7]. With the exception of *P. aeruginosa*, tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are sensitive to tigecycline [2-4, 7-11]. Tigecycline has shown to be highly effective against multi-resistant *Acinetobacter* spp., particularly *A. baumannii* that are commonly associated with serious nosocomial infections. Similar activity has been observed against *Enterobacteriaceae*, even extended-spectrum beta-lactamase (ESBL) and AmpC producing strains [10]. Tigecycline has demonstrated MIC$_{90}$ values of $\le$0.5 mcg/ml against methicillin-resistant *Staphylococcus aureus* (MRSA) and other gram-positive organisms [2, 4-6]. Tigecycline has shown potent activity in animal models infected with selected strains of multi-drug resistant *Enterococcus faecium* and *Enterococcus faecalis* [4,5] with diverse genotypes of vanA, vanB and vanC [6].

The T.E.S.T. program determined the in vitro activity of tigecycline compared to most commonly prescribed broad spectrum antimicrobials against gram-negative and gram-positive species collected from 484 hospitals in 53 countries from 2004 to 2008. This study was designed to evaluate the in vitro activity of tigecycline against multiple antimicrobials and shows the evaluation of its activity against levofloxicin resistant organisms.

METHODS

- For the T.E.S.T program all isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids, and other defined sources. Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using common broth microdilution panels. Only one isolate per patient was accepted.
- For this study 102,519 clinical isolates were collected from 2004 to 2008 from 484 hospitals in 53 countries.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [12]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): gram positive panel: amoxicillin/clavulanic acid (0.03/0.015-8/4, tested using a 2:1 ratio of amoxicillin:clavulanic acid; reported concentrations refer to amoxicillin); ampicillin (0.06-16); ceftriaxone (0.03-64); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.06-32); minocycline (0.25-8); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.25/4-16/4) and vancomycin (0.12-32); gram-negative panel: amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16, tested using a 2:1 ratio of amoxicillin:clavulanic acid; reported concentrations refer to amoxicillin); ampicillin (0.5-32); cefepime (0.5-32); ceftriaxone (0.06-64); ceftazidime (8-32); imipenem (0.06-16; levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16) and piperacillin/tazobactam (0.06/4-128/4).
- MIC interpretive criteria for all drugs except tigecycline followed published guidelines established by the CLSI where applicable [12]. MIC interpretive criteria for tigecycline followed criteria established by the Federal Drug Administration (FDA, United States, 2005) where applicable [13].
- *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone were >1 mcg/ml and/or ceftazidime were >8 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: cefotaxime (30-mcg), cefotaxime/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.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains where applicable: *Enterococcus faecalis* ATCC 29212; *Escherichia coli* ATCC 25922; *Escherichia coli* ATCC 35218; *Klebsiella pneumoniae* ATCC 700603 (as positive ESBL control); *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *Staphylococcus aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *Pseudomonas aeruginosa* ATCC 27853.
- The collection and transportation of organisms, confirmation of identification were conducted by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL, USA).

RESULTS

Table 1. In vitro activity of tigecycline and comparative agents against selected levofloxicin resistant gram-negative organisms.

Organism (n)	Antimicrobial	%S[a]	MIC$_{50}$ (mgc/mL)	MIC$_{90}$ (mgc/mL)
Enterobacteriaceae spp. (6,650)	Tigecycline	93.2	0.5	2
	Amikacin	89.7	4	32
	AmoxClav	28.2	16	>32
	Ampicillin	4.5	>32	>32
	Cefepime	66.2	2	>32
	Ceftriaxone	47.4	16	>64
	Imipenem	98.6	0.25	1
	Levofloxacin	0	>8	>8
	Minocycline	54.2	4	>16
	PipTazo	62.4	8	>128
E coli (3,596)	Tigecycline	100	0.25	0.5
	Amikacin	96.7	2	8
	AmoxClav	42.3	16	32
	Ampicillin	8.1	>32	>32
	Cefepime	77.4	$\le$0.5	>32
	Ceftriaxone	67.2	0.12	>64
	Imipenem	99.8	0.25	0.5
	Levofloxacin	0	>8	>8
	Minocycline	63.4	4	16
	PipTazo	85.3	2	64
Klebsiella spp. (1,697)	Tigecycline	88.9	1	4
	Amikacin	78.1	8	64
	AmoxClav	19.1	32	>32
	Ampicillin	0.2	>32	>32
	Cefepime	43.3	16	>32
	Ceftriaxone	23.3	>64	>64
	Imipenem	95.6	0.5	2
	Levofloxacin	0	>8	>8
	Minocycline	51.6	4	>16
	PipTazo	35.4	128	>128
ESBL-producers[b] (1,619)	Tigecycline	94.6	0.5	2
	Amikacin	84.2	8	32
	AmoxClav	18.4	16	>32
	Ampicillin	0.2	>32	>32
	Cefepime	30.3	32	>32
	Ceftriaxone	8.8	>64	>64
	Imipenem	97.4	0.25	1
	Levofloxacin	0	>8	>8
	Minocycline	57.5	4	>16
	PipTazo	53.2	16	>128
Enterobacter spp. (1,175)	Tigecycline	80.1	1	4
	Amikacin	86.3	4	32
	AmoxClav	2.2	>32	>32
	Ampicillin	0	>32	>32
	Cefepime	63.7	8	>32
	Ceftriaxone	20.9	64	>64
	Imipenem	98.5	0.5	1
	Levofloxacin	0	>8	>8
	Minocycline	31.5	8	>16
	PipTazo	32.2	64	>128
Acinetobacter spp.(2,831)	Tigecycline	na	1	2
	Amikacin	49.3	32	>64
	Cefepime	8.2	32	>32
	Ceftriaxone	2.6	>64	>64
	Imipenem	66	2	>16
	Levofloxacin	0	>8	>8
	Minocycline	78.2	1	8
	PipTazo	14.3	128	>128
P. aeruginosa (3,213)	Tigecycline	na	16	>16
	Amikacin	78.9	8	64
	Cefepime	43.3	16	>32
	Ceftriaxone	7.6	>64	>64
	Imipenem	60	4	16
	Levofloxacin	0	>8	>8
	Minocycline	2.6	>16	>16
	PipTazo	69.5	32	>128

[a]Susceptibilities are defined in CLSI document M100-S18 (2008) where applicable. Tigecycline breakpoints are defined in FDA package insert (Tygacil®, 2005).
[b]ESBL producing *E. coli*, *K. pneumoniae* and *K. oxytoca*.

Table 2. In vitro activity of tigecycline and comparative agents against selected levofloxicin resistant gram-positive organisms.

Organism	Antimicrobial	%S[a]	MIC$_{50}$ (mgc/mL)	MIC$_{90}$ (mgc/mL)
S. aureus (methicillin sensitive) (1,257)	Tigecycline	100	0.12	0.25
	AmoxClav	99.5	0.5	2
	Ampicillin	88.5	0.25	16
	Ceftriaxone	98.9	4	8
	Imipenem	100	$\le$0.12	0.25
	Levofloxacin	0	16	>32
	Linezolid	100	2	4
	Minocycline	98.4	$\le$0.25	0.5
	Penicillin	86.3	0.12	>8
	PipTazo	98.9	0.5	1
	Vancomycin	100	1	1
S. aureus (methicillin resistant) (407)	Tigecycline	99.8	0.12	0.25
	AmoxClav	1.9	8	>8
	Ampicillin	0	>16	>16
	Ceftriaxone	0.9	64	>64
	Imipenem	0.5	1	>16
	Levofloxacin	0	16	>32
	Linezolid	100	2	4
	Minocycline	95.8	<0.25	4
	Penicillin	0	>8	>8
	PipTazo	2.5	>16	>16
	Vancomycin	100	1	1
E. faecalis (2,014)	Tigecycline	99.7[b]	0.12	0.25
	Ampicillin	99.8	1	2
	Levofloxacin	0	32	>32
	Linezolid	98.9	1	2
	Minocycline	43.3	8	>8
	Penicillin	99.4	4	8
	Vancomycin	91.9	1	2
E. faecium (1,681)	Tigecycline	100[b]	0.06	0.12
	Ampicillin	4.8	>16	>16
	Levofloxacin	0	>32	>32
	Linezolid	95.4	2	2
	Minocycline	73.4	$\le$0.25	8
	Penicillin	4.3	>8	>8
	Vancomycin	44.1	>32	>32
VRE[c] (1,069)	Tigecycline	99.9[b]	0.06	0.12
	Ampicillin	15.2	>16	>16
	Levofloxacin	0	>32	>32
	Linezolid	95.6	2	2
	Minocycline	70	0.5	8
	Penicillin	14.7	>8	>8
	Vancomycin	0	>32	>32

[a]Susceptibilities are defined in CLSI document M100-S18 (2008) where applicable. Tigecycline breakpoints are defined in FDA package insert (Tygacil®, 2005).
[b]Tigecycline breakpoints are defined in FDA package insert (Tygacil®, 2005)as susceptible less than or equal to 0.25 mcg/mL for vancomycin-susceptible *E. faecalis*. This breakpoint was expanded to include all enterococci for comparative purposes only.
[c]Vancomycin-resistant *E. faecium* and *E. faecalis*.

CONCLUSIONS

- While levofloxacin resistance in this study varied according to organism type, the overall percentage of resistance was 14.3% (14,690/102,519).
- Tigecycline has limited activity against *P. aeruginosa*, but excellent in vitro activity against *Acinetobacter* spp. with the lowest MIC$_{50/90}$ (1/2 mcg/mL) of all antimicrobials tested.
- For levofloxacin resistant *Enterobacteriaceae*, including ESBL producers, tigecycline MIC$_{50/90}$ values were 0.5/2 mcg/mL, comparable to those of imipenem (0.25/1 mcg/mL).
- Against levofloxacin resistant gram-positive organisms, including MRSA and VRE, tigecycline showed excellent in vitro activity, with tigecycline MIC$_{90}$ values of $\le$0.25 mcg/mL. 99.8% of MRSA and VRE were susceptible to tigecycline.
- Tigecycline demonstrated broad spectrum in vitro activity against levofloxacin resistant pathogens, and should prove to be a useful addition to hospital formularies against these potentially difficult-to-treat isolates.

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