#P1-006

Comparison of Antimicrobial Susceptibility of Isolates From Various Body Sites: Asia/Pacific Results From the Tigecycline Evaluation Surveillance Trial (TEST) 2004-2006

R. Badal[1], S. Bouchillon[1], B. Johnson[1], T. Stevens[1], J. Johnson[1], D. Hoban[1], M. Dowzicky[2]

[1]International Health Management Associates, Schaumburg, IL, USA

[2]Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL 60173
Tel: (847) 303-5003
Fax: (847) 303-5601
www.ihmainc.com

REVISED ABSTRACT

Background: One of the goals of surveillance studies is to identify changing patterns of bacterial resistance to help guide current therapy. The Tigecycline Evaluation Surveillance Trial (TEST) is an ongoing global study that can serve to help recognize current trends in resistance on many levels. This report evaluates differences in susceptibility of strains from different body sites, collected in Asia/Pacific 2004-2006. **Methods:** 1,509 strains isolated from 10 specimen types were collected and identified from 2004-2006 at 9 hospitals in 7 countries in Asia/Pacific. MICs for each strain were determined per CLSI guidelines at each facility using broth microdilution. $MIC_{50/90}$ values were analyzed to identify any significant differences in antibiograms from different sources. **Results:** Tigecycline (TIG) MIC_{50} values for almost all organism/specimen pairings were +/- 2 dilutions of each other, with no single source routinely giving a higher MIC_{50} than others. The same was seen for TIG MIC_{90} values, which were almost always within 1-2 dilutions of the MIC_{50}. Comparator drugs generally showed more variability in activity vs. isolates from various body sites, and their MIC_{90}/MIC_{50} ratios were often much higher than those of TIG. **Conclusion:** Bacteria isolated from more than 10 different body sites had generally similar antibiograms, with no single source showing significantly different sensitivity patterns. TIG demonstrated a broad spectrum of activity and consistently low MIC_{90}/MIC_{50} ratios, including strains resistant to other drugs (MRSA, ESBL-producers, imipenem-resistant Acinetobacter, etc.), clearly reinforcing its position as a viable alternative for therapy of difficult-to-treat infections.

INTRODUCTION

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 considered a bacteriostatic agent, it has shown some bactericidal activity against key pathogens [1,2]. Tigecycline was developed to provide activity against tetracycline- and multi-drug-resistant pathogens and has demonstrated significant 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 of less than 10^{-9} observed [3, 5, 7]. Tetracycline-resistant bacteria with either tetracycline efflux pumps or ribosomal protective features are usually sensitive to tigecycline [2-4, 7-11], except for *Pseudomonas aeruginosa*. Tigecycline has been 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*, including most extended-spectrum beta-lactamase (ESBL) producing strains [10]. Tigecycline has demonstrated MIC_{90} values of ≤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 van-A, -B and -C [6].

With such a broad spectrum of activity, tigecycline has the potential to be useful in a variety of infections. This report describes the in vitro activity of tigecycline against a large, diverse population of clinical isolates collected from various specimen types in hospitals in Western Europe from 2004 through 2006.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, fluids and few other defined sources. Only one isolate per patient was accepted.
- 6,936 clinical isolates were collected and tested between January 2004 and June 2006 from 9 study centers in 7 countries in Asia.
- Custom broth microdilution panels were supplied by MicroScan (Dade Behring Inc., Sacramento, CA, USA) with the following antimicrobial agents and concentrations (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12-32); piperacillin/tazobactam (0.06-128); levofloxacin (0.008-8); ceftriaxone (0.06-64); cefepime (0.5-32); ampicillin (0.5-32); amikacin (0.5-64); minocycline (0.5-16); ceftazidime (8-32); tigecycline (0.008-16); and imipenem (0.06-16).
- MIC interpretive criteria followed published guidelines established by the CLSI where applicable [12]. Tigecycline breakpoints (in units of mcg/ml), as approved by the US Food and Drug Administration (FDA), are defined as follows: *Enterobacteriaceae*: susceptible ≤2, intermediate =4, and resistant ≥8; *Staphylococcus aureus* (including MRSA): susceptible ≤0.5, no intermediate or resistant breakpoints; *Enterococcus faecalis* (vancomycin-susceptible): susceptible ≤0.25, no intermediate or resistant breakpoints; non-pneumococcal streptococci: susceptible ≤0.25, no intermediate or resistant breakpoints.
- Isolates were identified to genus and species by the local laboratory. Each site tested the isolates using broth microdilution.
- Quality control of broth microdilution panels followed manufacturer's and CLSI guidelines using the following ATCC strains: *E. faecalis* ATTC 29212; *Escherichia coli* ATCC 25922; *Haemophilus influenzae* ATCC 49247; *Haemophilus influenzae* ATCC 49766; *S. aureus* ATCC 29213; *Streptococcus pneumoniae* ATCC 49619; and *P. aeruginosa* ATCC 27853.
- The collection and transportation of organisms and the confirmation of identification, as well as construction and management of a centralized database, were conducted and coordinated by Laboratories International for Microbiology Studies (LIMS), a subsidiary of International Health Management Associates, Inc. (IHMA, Schaumburg, IL).

REFERENCES

1. Sum, P.E. and P. Petersen, *Synthesis and structure-activity relationship of novel glycylcycline derivatives leading to the discovery of GAR-936*. Bioorg Med Chem Lett, 1999. 9(10): p. 1459-62.
2. Abbanat, D., M. Macielag, and K. Bush, *Novel antibacterial agents for the treatment of serious Gram-positive infections*. Expert Opin Investig Drugs, 2003. 12(3): p. 379-99.
3. Betriu, C., et al., *In vitro activities of tigecycline (GAR-936) against recently isolated clinical bacteria in Spain*. Antimicrob Agents Chemother, 2002. 46(3): p. 892-5.
4. Gales, A.C. and R.N. Jones, *Antimicrobial activity and spectrum of the new glycylcycline, GAR-936 tested against 1,203 recent clinical bacterial isolates*. Diagn Microbiol Infect Dis, 2000. 36(1): p. 19-36.
5. Henwood, C.J., et al., *Antibiotic resistance among clinical isolates of Acinetobacter in the UK, and in vitro evaluation of tigecycline (GAR-936)*. J Antimicrob Chemother, 2002. 49(3): p. 479-87.
6. Chopra, I., *New developments in tetracycline antibiotics: glycylcyclines and tetracycline efflux pump inhibitors*. Drug Resist Updat, 2002. 5(3-4): p. 119-25.
7. Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycylcycline antibacterial agent*. Pharmacotherapy, 2000. 20(9 Pt 2): p. 219S-223S; discussion 224S-228S.
8. Biedenbach, D.J., M.L. Beach, and R.N. Jones, *In vitro antimicrobial activity of GAR-936 tested against antibiotic-resistant gram-positive blood stream infection isolates and strains producing extended-spectrum beta-lactamases*. Diagn Microbiol Infect Dis, 2001. 40(4): p. 173-7.
9. Patel, R., et al., *In vitro activity of GAR-936 against vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus and penicillin-resistant Streptococcus pneumoniae*. Diagn Microbiol Infect Dis, 2000. 38(3): p. 177-9.
10. Petersen, P.J., et al., *In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936)*. Antimicrob Agents Chemother, 1999. 43(4): p. 738-44.
11. Petersen, P.J., et al., *In vitro and in vivo activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate Staphylococcus aureus and other resistant gram-positive pathogens*. Antimicrob Agents Chemother, 2002. 46(8): p. 2595-601.
12. Clinical and Laboratory *Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Sixteenth Informational Supplement*. CLSI document M100-S16. Wayne, PA, 2006.

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

Table 1. Tigecycline MIC_{50} and MIC_{90} (mcg/ml) for gram-negative isolates with n>=10 from various body sites[a]. (GI = Gastrointestinal; GU = Genitourinary; HEENT = Head, Ears, Eyes, Nose, Throat; Resp = Respiratory; SSS = Skin/Soft Tissue)

Organism		Blood	GI	GU	HEENT	Resp	SSS
E. coli	(n)	(81.00)	(13.00)	(61.00)		(15.00)	(22.00)
	MIC_{50}	0.12	0.12	0.12		0.12	0.12
	MIC_{90}	0.25	0.25	0.50		0.50	0.25
Klebsiella spp.	(n)	(56.00)		(61.00)		(62.00)	(11.00)
	MIC_{50}	0.50		0.50		0.50	0.25
	MIC_{90}	2.00		1.00		1.00	0.50
ESBL-producers	(n)	(27.00)		(23.00)		(18.00)	
(*E. coli, Klebsiella spp.*)	MIC_{50}	0.50		0.50		0.50	
	MIC_{90}	2.00		0.50		1.00	
Enterobacter spp.	(n)	(28.00)		(39.00)		(53.00)	(38.00)
	MIC_{50}	0.50		0.50		0.50	0.50
	MIC_{90}	2.00		2.00		1.00	1.00
Serratia spp.	(n)	(13.00)		(13.00)		(31.00)	(10.00)
	MIC_{50}	1.00		1.00		1.00	1.00
	MIC_{90}	2.00		1.00		1.00	2.00
P. aeruginosa	(n)	(12.00)		(14.00)	(14.00)	(65.00)	(44.00)
	MIC_{50}	8.00		8.00	8.00	8.00	8.00
	MIC_{90}	>16		16.00	16.00	16.00	>16
Acinetobacter spp.	(n)	(35.00)		(10.00)		(40.00)	(19.00)
	MIC_{50}	0.12		0.12		0.12	0.25
	MIC_{90}	0.50		0.50		1.00	1.00
H. influenzae	(n)				(12.00)	(89.00)	
	MIC_{50}				0.12	0.12	
	MIC_{90}				0.25	0.25	
H. influenzae	(n)					(19.00)	
(B-lac positive)	MIC_{50}					0.12	
	MIC_{90}					0.25	

[a] $MIC_{50/90}$ not calculated if n<10.

Table 2. Tigecycline MIC_{50} and MIC_{90} (mcg/ml) for gram-positive isolates with n>=10 from various body sites[a].

Organism		Blood	GI	GU	HEENT	Resp	SSS
S. aureus	(n)	(14.00)			(11.00)	(47.00)	(112.00)
	MIC_{50}	0.25			0.12	0.12	0.12
	MIC_{90}	0.50			0.12	0.50	0.25
S. aureus	(n)					(36.00)	(36.00)
MRSA only	MIC_{50}					0.25	0.12
	MIC_{90}					0.50	0.25
Enterococcus spp. [b]	(n)	(28.00)	(39.00)	(53.00)			(38.00)
	MIC_{50}	0.12	0.06	0.12			0.12
	MIC_{90}	0.12	0.12	0.12			0.25
S. pneumoniae	(n)	(30.00)				(62.00)	
	MIC_{50}	0.03				0.12	
	MIC_{90}	0.50				0.50	
S. pneumoniae	(n)					(17.00)	
(pen-intermed.)	MIC_{50}					0.06	
	MIC_{90}					0.50	
S. pneumoniae	(n)					(10.00)	
(pen-resistant)	MIC_{50}					0.02	
	MIC_{90}					1.00	
S. agalactiae	(n)			(42.00)			(10.00)
	MIC_{50}			0.03			0.06
	MIC_{90}			0.06			0.06

[a] $MIC_{50/90}$ not calculated if n<10.
[b] Includes 3 VR *E. faecium*, for which $MIC_{min/max}$ were 0.03-0.06.

Tables 3a - 3h. Drugs with MIC_{50} or MIC_{90} varying by >2 log2 dilutions among specimen sources (n>=10). Ak=amikacin, Am=ampicillin, AUG=amoxicillin/clavulanic acid, Cax=ceftriaxone, Caz=ceftazidime, Cpe=cefepime, Imp=imipenem, Lvx=levofloxacin, Min=minocycline, P=penicillin, P/T=piperacillin/tazobactam, Va=vancomycin.

Table 3a. *E. coli* $MIC_{50/90}$

Source (n)	Cpe	Cax	Lvx	P/T
Blood (81)	≤0.5/4	≤0.06/32	0.03/>8	1/4
GI (13)	2/>32	4/>64	0.5/>8	1/16
GU (61)	≤0.5/32	≤0.06/>64	4/>8	1/16
Resp (15)	≤0.5/32	2/>64	8/>8	2/8
SSS (22)	≤0.5/8	≤0.06/64	0.12/>8	1/2

Table 3b. *Klebsiella* spp. $MIC_{50/90}$

Source (n)	Cpe	Lvx	Min	P/T
Blood (56)	≤0.5/>32	0.06/8	2/>16	2/64
GU (61)	≤0.5/8	0.03/2	2/4	2/128
Resp (62)	≤0.5/4	0.06/8	2/8	2/4
SSS (11)	≤0.5/16	0.06/0.5	2/4	2/8

Table 3c. *Enterobacter* spp. $MIC_{50/90}$

Source (n)	Cax	Lvx
Blood (28)	0.25/>64	0.06/8
GU (39)	0.25/>64	0.06/8
Resp (53)	2/>64	0.06/4
SSS (38)	2/>64	0.06/1

Table 3d. *Serratia* spp. $MIC_{50/90}$

Source (n)	Ak	Cpe	Caz	Cax	P/T
Blood (13)	4/>64	≤0.5/>32	≤8/>32	0.5/>64	2/4
GU (13)	2/4	≤0.5/≤0.5	≤8/≤8	0.25/2	1/4
Resp (31)	2/4	≤0.5/2	≤8/≤8	0.5/8	2/16
SSS (10)	2/4	≤0.5/≤0.5	≤8/≤8	0.25/0.5	2/2

Table3e. *Acinetobacter* spp. $MIC_{50/90}$

Source (n)	Imp	Lvx	P/T
Blood (35)	0.25/>16	0.12/4	1/>128
GU (10)	0.5/2	0.06/8	4/16
Resp (40)	0.25/16	0.25/8	2/>128
SSS (19)	0.5/16	2/>8	2/>128

Table 3f. *Pseudomonas aeruginosa* $MIC_{50/90}$

Source (n)	Ak	Caz	Imp
Blood (12)	4/4	≤8/≤8	1/1
GU (14)	4/64	≤8/>32	1/8
HEENT (14)	4/32	≤8/≤8	1/8
Resp (65)	4/16	≤8/>32	1/8
SSS (44)	4/64	≤8/>32	1/16

Table 3g. *Streptococcus pneumoniae* $MIC_{50/90}$

Source (n)	P	P/T
Blood (30)	≤0.06/0.25	≤0.25/≤0.25
Resp (62)	≤0.06/2	≤0.25/2

Table 3h. *Staphylococcus aureus* $MIC_{50/90}$

Source (n)	Aug	Cax	Imp	Lvx	Min	P/T
Blood (14)	1/>8	4/>64	0.25/>16	0.25/8	≤0.25/8	1/>16
HEENT (11)	1/>8	4/>64	0.25/>16	0.25/>32	≤0.25/4	1/>16
Resp (47)	>8/>8	>64/>64	16/>16	8/>32	2/8	>16/>16
SSS (112)	1/>8	4/>64	0.25/1	0.25/4	≤0.25/4	1/>16

CONCLUSIONS

- Tigecycline MIC_{50} and MIC_{90} values for each species/group were within 2 $\log_2$ dilutions, demonstrating remarkable consistency regardless of specimen source.
- Tigecycline MIC_{90} values were within 1-2 $\log_2$ dilutions of the MIC_{50} in the vast majority of the cases presented; however, *S. pneumoniae* $MIC_{90/50}$ ratios ranged from 4 to 64.
- Although MIC_{50} values for comparator drugs were often within 2 doubling dilutions across specimen sources, there were numerous exceptions to this, and MIC_{90}s frequently varied by more than 2 $\log_2$ dilutions across specimen sources. This was due less to any particular specimen source than to the relative percentage of resistant isolates recovered from each source.
- Tigecycline's consistent activity against most strains in this study, including those resistant to one or more other antimicrobics, indicates that it could be very useful in treatment of serious infections in Asia, as in other regions of the world.