Tigecycline Antimicrobial Susceptibility Testing in the Asia-Pacific (APAC) Region: Report from the SENTRY Antimicrobial Surveillance Program (2006)

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AMENDED ABSTRACT

Background:
Tigecycline (TGC) is the first clinically used glycylcycline and it possesses activity against key Gram-positive and -negative bacterial pathogens. It evades acquired efflux and target-mediated resistances to common tetracyclines. As multi-drug resistant (MDR) *Acinetobacter* spp., ESBL-producing Enterobacteriaceae, methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant enterococci (VRE) are common in the APAC region; we examined the activity of TGC and compared three testing methods on a diverse collection of recent clinical isolates.

Methods:
Thirty seven institutions from 10 countries contributed strains, collected as part of the SENTRY Program (2006). All isolates were tested against TGC using validated commercial dry-form broth microdilution (BMD) panels (TREK), with concurrent quality controls and CLSI interpretations of comparison agents. TGC breakpoints published by the US-FDA were applied for each indicated species. TGC disk diffusion and Etest results were also generated.

Results:
A total of 4,430 (1,440 Gram-negative and 2,990 Gram-positive) isolates were received. Apart from the Proteae, >99% of Enterobacteriaceae, including strains with ESBLs, had TGC MICs at ≤2 mg/L. Modal TGC MIC values for enterococci and staphylococci were only 0.12 mg/L, with 100% ≤0.5 mg/L. The presence of tetracycline resistance determinants resulted in minimal elevations of TGC MIC results, most notably in MRSA. For *A. baumannii*, MICs ranged from ≤0.03 to >4 mg/L, but 98% were inhibited at ≤2 mg/L including the 49.7% of strains with presumptive carbapenemases.

Conclusion:
TGC appears to be effective in vitro against recent clinical isolates from the APAC Region including prevalent MDR strains and those harbouring resistances to often reserved agents.

INTRODUCTION

Tigecycline is the first glycylcycline for clinical use and possesses a broad range of activity against major Gram-positive and -negative bacterial pathogens. Its major asset is its ability to evade acquired efflux and target-mediated resistances to common tetracyclines. Multi-drug resistance (MDR) is very common in the APAC region in many important pathogens including *Acinetobacter* spp., ESBL-producing Enterobacteriaceae, methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant enterococci (VRE). Hence, we examined the activity of tigecycline and compared three testing methods on a diverse collection of recent clinical isolates from this region.

MATERIALS AND METHODS

Bacterial Isolates:

- Non-duplicate clinically significant patient isolates were submitted from 37 medical centres in ten countries (Australia 5 sites; China 10; Thailand 1; Korea 3; Taiwan 2; Hong Kong 1; Singapore 1; Philippines 2; India 10; Indonesia 3).
- Species identification was confirmed in a central laboratory (Women's and Children's Hospital, Adelaide, Australia) using reference methodologies, where necessary.

Susceptibility Tests:

- Isolates were tested against tigecycline using validated dry-form broth microdilution MIC panels with cation-adjusted Mueller-Hinton broth (TREK Diagnostic Systems; East Grinstead, UK). Testing, incubation and MIC interpretation were performed using the manufacturer's recommendations and/or CLSI guidelines (1, 2).
- Quality control strains utilized included *Escherichia coli* ATCC 25922 and 35218, *Pseudomonas aeruginosa* ATCC 27853, *S. aureus* ATCC 29213 and *Streptococcus pneumoniae* ATCC 49619; all MIC results were within CLSI specified ranges.
- Isolates were also tested by disk diffusion and Etest® (AB BIODISK; Solna, Sweden) strips according to the manufacturer's instructions.

ANALYSIS

- Data were analysed for MIC_{50}, MIC_{90} and percentage susceptible and resistant according to FDA package insert interpretive criteria (2005), and comparisons between broth microdilution and Etest® MIC values were made.

RESULTS

- A total of 4,430 (2,990 Gram-negative and 1,440 Gram-positive) isolates were evaluated.
- The prevalence of screen-positive ESBL strains was extremely high among *E. coli* (40%) and *K. pneumoniae* (44%).
- Apart from the Proteae, >99% of Enterobacteriaceae, including screen-positive ESBL *E. coli* and *Klebsiella pneumoniae* strains, had tigecycline MICs at ≤2 mg/L (Table 1).
- Modal tigecycline MIC values for enterococci and staphylococci were only 0.12 mg/L, with 100% of strains inhibited at tigecycline MIC ≤0.5 mg/L.
- The presence of tetracycline resistance determinants resulted in minimal elevations of tigecycline MIC results, most notably in MRSA.
- For *A. baumannii*, MIC values ranged from ≤0.06 to >4 mg/L, but 98% were inhibited at ≤2 mg/L including the 35% of strains with presumptive carbapenemases.
- Tigecycline Etest MIC values were generally higher (0.5 double dilution) for Enterobacteriaceae compared to broth microdilution results. Overall, 79% of results were within ± 1 double dilution and >99% within 2 double dilutions (Table 2). For Gram-positive isolates, tigecycline Etest MIC values were slightly lower than broth microdilution results, with over 85% of enterococci and >90% of staphylococci within ± 1 double dilution.
- Etest results for *E. faecalis* were significantly lower than those of broth microdilution methods due to difficulties with reading 80% endpoints for this species (Table 2).

CONCLUSION

- Tigecycline appears to be effective in vitro against recent clinical isolates from the Asia-Pacific region including prevalent multi-drug resistant strains and those harbouring resistances to often reserved agents.

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Table 1. Activity of tigecycline against Gram-negative and Gram-positive pathogens collected as part of the Asia-Pacific SENTRY Surveillance Program (2006).

	MIC (mg/L)		Number of isolates inhibited at MIC (mg/L):									% by category:[a]	
Organism (number tested)	50%	90%	≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4	Susceptible	Resistant
Enterobacteriaceae (857)	0.25	1		24	166	321	259	71	14	2		99.8	0.0
Escherichia coli (329)	0.12	0.5		23	145	122	38	1				100.0	0.0
ESBL screen-negative (196)	0.12	0.25		22	98	63	12	1				100.0	0.0
ESBL screen-positive (133)	0.25	0.5		1	47	59	26					100.0	0.0
Klebsiella pneumoniae (292)	0.5	1			2	105	134	43	7	1		99.7	0.0
ESBL screen-negative (162)	0.5	1			2	77	63	16	4			100.0	0.0
ESBL screen-positive (130)	0.5	1				28	71	27	3	1		99.2	0.0
Enterobacter spp. (92)	0.5	1			1	33	46	7	4	1		98.9	0.0
Acinetobacter baumannii (163)	0.5	1	3	14	30	20	45	42	6	2	1	98.2	0.0
imipenem-susceptible (81)	0.12	1	3	14	24	15	16	7	3			100.0	0.0
imipenem-resistant (82)	1	1			6	5	29	35	3	2	1	96.3	0.0
Staphylococcus aureus (1,545)	0.12	0.25	7	275	714	468	79	2				99.9	-[b]
oxacillin-susceptible (884)	0.12	0.25	5	217	454	201	7					100.0	-
oxacillin-resistant (661)	0.25	0.5	2	58	260	267	72	2				99.7	-
Enterococcus spp. (614)	0.12	0.25	26	136	300	142	10					98.4	-
Streptococcus pneumoniae (256)	≤0.03	≤0.03	252	3	1							100.0	-

a. US-FDA package insert breakpoints (2005) applied.
b. No criteria for this category has been proposed.

Table 2. Broth microdilution (BMD) MIC versus Etest MIC results for tigecycline.

	Fold dilution difference between Etest and BMD MIC[a]									% within:	
Organism (number evaluated)[b]	≤-2	-1.5	-1	-0.5	0	0.5	1	1.5	≥2	±1	±2
Enterococcus faecium (216)	8	54	45	80	25	4				96.3	99.1
Enterococcus faecalis (355)	80	69	83	57	54	11	1			77.5	99.4
Staphylococcus aureus (1,538)	137	219	382	364	226	186	21	3		90.9	99.6
Coagulase-negative staphylococci (293)	8	27	56	89	78	30	4	1		96.9	100.0
Enterobacteriaceae[c] (855)		2	13	68	122	268	203	142	37	79.1	99.8
Escherichia coli (328)		2	8	45	62	114	64	30	3	89.9	100.0
Enterobacter spp. (92)			1	3	23	24	26	12	3	83.7	100.0
Klebsiella spp. (326)			2	14	28	97	86	79	20	69.6	100.0

a. Positive values indicate Etest MIC greater than BMD MIC.
b. On-scale values only included.
c. Excluding Proteae.

SELECTED REFERENCES

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