

Evaluating Multidrug Resistant (MDR) *Acinetobacter* Isolates from Latin American Countries: The T.E.S.T. Program

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REVISED ABSTRACT

Background: Tigecycline (TIG), a member of a new class of antimicrobials (glycylcyclines), has been shown to have potent expanded 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 compared to piperacillin-tazobactam (PT), levofloxacin (LVX), ceftriaxone (CAX), cefepime (CPE), amikacin (AK), minocycline (MIN), ceftazidime (CAZ) and imipenem (IMP) against multidrug resistant *Acinetobacter* strains collected from 10 sites in Latin America throughout 2004-2007. **Methods:** A total of 128 clinical isolates of *Acinetobacter* spp. were identified to the species level at each local site and confirmed by the central laboratory. MICs were determined by the local laboratory using broth microdilution panels according to CLSI guidelines. **Results:** Resistance rates to the comparator drugs against all *Acinetobacter* were CAX 70%, CAZ 66%, LVX 49%, CPE 34%, PT 58%, AK 23%, IMP 2.2%, and MIN 2.3%. Strains were grouped by presence of resistance to 0, 1, 2, 3, 4 or ≥ 5 drug classes. The percentage of strains falling into Groups 0 through 5 were 20%, 12%, 12%, 28%, 23%, and 5%, respectively. TIG inhibited $>96\%$ of strains in each Group 0 - 4 at 2 mcg/ml and 100% in Group 5 at 4 mcg/ml. TIG MIC_{50/90} for Groups 0-5 were 0.25/1, 0.25/2, 0.25/2, 0.25/2, 0.25/0.5 and 0.5/4 mcg/ml, respectively. **Conclusion:** Although resistance to one or two drug classes increased the TIG MIC₉₀ by 2-fold, and resistance to ≥ 5 drug classes increased MIC₉₀ values by 4-fold, TIG maintained MIC values below 2 mcg/ml in over 97% of the multidrug resistant *Acinetobacter* isolates. Other studies have shown that existing non-specific efflux pumps may pump TIG. Overall, TIG's in vitro activity against multidrug resistant *Acinetobacter* should prove useful in therapy of infections caused by such strains.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycylcyclines. 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 it and other glycylcyclines 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 restored 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.

Infections secondary *Acinetobacter* present a challenge to clinicians with increasing multidrug resistance worldwide. Resistance of *Acinetobacter* to cephalosporins, aminoglycosides and ciprofloxacin is now widespread but carbapenems, colistin, sulbactam and minocycline remain effective in over 80% of most strains [4, 5]. The emergence of imipenem resistance in this species is of considerable concern leaving relatively limited treatment options for infections due these resistant *Acinetobacter* and has led to a search for new compounds with activity against these problematic pathogens.

This study was undertaken to document the in vitro activity of tigecycline against multidrug resistant *Acinetobacter* in a diverse population from multiple investigative sites in Latin American countries. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

- All isolates were derived from blood, respiratory tract, urine, skin, wound, body fluids and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested between January 2004 - January 2007 from 10 sites in 6 Latin America countries, Guatemala, Honduras, Jamaica, Mexico, Panama and Puerto Rico. 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 [6]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents and dilution ranges (expressed in mcg/mL) were included on the panels: tigecycline (0.008-16), imipenem (0.06-16), levofloxacin (0.008-8), minocycline (0.5-16), piperacillin/tazobactam (0.06/4-128/4), amikacin (0.5-32), ceftazidime (8-32), ceftriaxone (0.06-64) and cefepime (0.5-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [7], where applicable. There are currently no breakpoints defined for tigecycline against *Acinetobacter* species.
- 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 and *Pseudomonas aeruginosa* ATCC 27853. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2007) guidelines [7].

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RESULTS

Results are shown in the following tables.

Table 1. Distribution of Multidrug Resistant *Acinetobacter* species in the Population Sample.

Organism	Total N	Percent (%) of Total N
<i>Acinetobacter baumannii</i>	98	76.5
<i>Acinetobacter calcoaceticus</i>	23	18
<i>Acinetobacter lwoffii</i>	5	3.9
<i>Acinetobacter</i> , non-speciated	2	1.6
Total	128	100

Multidrug resistance is defined as resistance to three or more CLSI drug classes.

Table 2. In Vitro Activity of Tigecycline and Comparators against 128 Multidrug Resistant Isolates of *Acinetobacter* from the Population Sample.

Drug	%Sus ^a	%Int	%Res	MIC (mcg/mL)		
				MIC ₅₀	MIC ₉₀	Range
Tigecycline	na	na	na	0.25	2	≤ 0.008 - 4
Amikacin	58.6	18	23.4	16	64	≤ 0.5 - >64
Cefepime	41.4	24.2	34.4	16	>32	≤ 0.5 - >32
Ceftazidime	25.8	8.6	65.6	32	>32	≤ 8 - >32
Ceftriaxone	11.7	18.8	69.5	>64	>64	≤ 0.06 - >64
Imipenem	97.8	0	2.2	1	2	0.25 - >16
Levofloxacin	31.3	19.5	49.2	4	>8	0.03 - >8
Minocycline	89.1	8.6	2.3	≤ 0.5	8	≤ 0.5 - 16
PipTazo	28.1	14.1	57.8	128	>128	≤ 0.06 - >128

Multidrug resistance is defined as resistance to three or more CLSI drug classes.

^aInterpretive criteria as defined by CLSI, M100-S17 (2007).

CONCLUSIONS

- Tigecycline had an in vitro MIC₉₀ of 2 mcg/ml against all multidrug resistant strains of *Acinetobacter*. This value was equivalent to imipenem and 8- to 16-fold lower than levofloxacin, cefepime, ceftazidime and amikacin.
- Tigecycline inhibited 96.7% (no table) of all multidrug resistant (resistant to three or more drug classes) *Acinetobacter* strains at a MIC of 2 mcg/mL.
- The MIC₅₀ and MIC₉₀ values of all study drugs increased as *Acinetobacter* species became resistant to more drug classes. The MIC₉₀ of tigecycline increase 2-fold with the introduction of one resistant drug class and again 2-fold between resistance to 4 or more drug classes.
- The in vitro activity of tigecycline was superior to imipenem, cefepime, ceftazidime, ceftriaxone, levofloxacin, minocycline and piperacillin-tazobactam against all *Acinetobacter* resistant to three or more drug classes.
- The in vitro activity of tigecycline in this study suggests that tigecycline is a potent antimicrobial agent that may be beneficial in the treatment of infections due to difficult to treat drug resistant and multidrug resistant *Acinetobacter*.