TÜBİTAK

ORIGINAL ARTICLE

Turk J Med Sci
2008; 38 (6): 583-586
© TÜBİTAK
E-mail: medsci@tubitak.gov.tr

In Vitro Activity of Tigecycline Against *Acinetobacter baumannii* Strains Isolated From Nosocomial Infections

Esragül AKINCI[1]
İpek MUMCUOĞLU[2]
Pınar ÖNGÜRÜ[1]
F. Nurhayat BAYAZIT[1]
Sevinç ERSOY ŞEN[1]
Ayşe ERBAY[1]
Neriman BALABAN[2]
Hürrem BODUR[1]

[1] Department of Clinic of Infectious Diseases and Clinical Microbiology, Ankara Numune Education and Research Hospital, Ankara - TURKEY

[2] Department of Microbiology and Clinical Microbiology, Ankara Numune Education and Research Hospital, Ankara - TURKEY

Aims: Acinetobacter species usually affect hospitalized patients and are involved in many infections associated with a high mortality rate. Management of infections caused by these strains is very difficult, as the strains often display multiple drug resistance, including carbapenem resistance. Tigecycline is the most recently developed semi-synthetic broad spectrum glycylcycline antibiotic. The present study was conducted to evaluate the in vitro susceptibility of *Acinetobacter baumannii* strains isolated from the hospitalized patients to tigecycline.

Materials and Methods: Acinetobacter isolates were collected from hospitalized patients with documented nosocomial infections between June 2005 and October 2006. Only one isolate per patient was accepted. Minimum inhibitory concentrations (MICs) were determined by E-test against tigecycline and other frequently used antibiotics.

Results: Overall, 98 *A. baumannii* isolates were collected from the cultures of nosocomially infected patients. Tigecycline was the most active agent against *A. baumannii* isolates among those tested, followed by netilmicin. MIC values of tigecycline were ≤2 µg/ml for 79 (80.6%) of the strains.

Conclusions: Tigecycline may have an important role in the treatment of nosocomial infections with multidrug-resistant Acinetobacter isolates, for which there are limited choices available for treatment.

Key Words: Tigecycline, Acinetobacter, antibiotic, resistance

Nozokomiyal İnfeksiyonlardan İzole Edilen *Acinetobacter baumannii* İzolatlarında Tigesiklinin İn Vitro Duyarlılığı

Problem: Acinetobacter suşları sıklıkla hastanede yatan hastalarda yüksek mortalite oranı ile seyreden infeksiyonlara neden olur. Bu suşların meydana getirdiği infeksiyonların tedavisi çok güçtür ve bu suşlar sıklıkla karbapenem direnci de dahil olmak üzere çoklu dirençlidirler. Tigesiklin son yıllarda geliştirilen, geniş spektrumlu, semisentetik bir glisiklin antibiyotiktir. Bu çalışma, hastanede yatan hastalardan izole edilen *Acinetobacter baumannii* suşlarında in vitro tigesiklin duyarlılığını değerlendirmek için yapılmıştır.

Materyal ve Metod: Çalışmada Haziran 2005 - Ekim 2006 tarihleri arasında hastane infeksiyonu dokümante edilen hastalardan izole edilen Acinetobacter suşları toplandı. Her bir hasta için sadece tek bir suş alındı. E-test ile tigesiklin ve diğer sık kullanılan antibiyotiklere karşı minimum inhibitör konsantrasyonları (MİK) belirlendi.

Bulgular: Hastane infeksiyonu olan hastaların kültürlerinden toplam 98 *A. baumannii* izolatı toplandı. *A. baumannii* suşlarına karşı tigesiklin en etkili antibiyotik idi. Bunu netilmisin izledi. Tigesiklin MİK değeri 79 (% 80.6) izolat için ≤2 µg/mL olarak bulundu.

Sonuç: Sınırlı tedavi seçeneği olan çoklu dirençli Acinetobacter izolatlarının neden olduğu infeksiyonların tedavisinde tigesiklin önemli bir rol oynayabilir.

Anahtar Sözcükler: Tigesiklin, Acinetobacter, antibiyotik, direnç

Received: September 21, 2007
Accepted: September 03, 2008

Correspondence
Esragül AKINCI
Department of Clinic of Infectious Diseases and Clinical Microbiology
Ankara Numune Education and Research Hospital,
Ankara - TURKEY

esragulakinci@yahoo.com

Introduction

Acinetobacter species usually affect hospitalized patients and are involved in many infections associated with a high mortality rate. Management of these infections is complicated by the emergence of strains resistant to most available antimicrobial agents, including carbapenems.

Tigecycline is the most recently developed semi-synthetic broad spectrum glycylcycline antibiotic. It has activity against a wide range of Gram-negative, Gram-positive and anaerobic bacteria, including strains with well-defined resistance

mechanisms. Tigecycline possesses activity against clinical isolates resistant to tetracyclines and multidrug-resistant pathogens. It has a different mechanism of interaction with the bacterial ribosome, which differentiates tigecycline from the structurally related tetracyclines and contributes to the enhanced clinical effectiveness of this agent (1,2).

The present study was conducted to evaluate the *in vitro* susceptibility of *Acinetobacter baumannii* strains isolated from hospitalized patients to tigecycline and compare with the susceptibility to the other most commonly used antimicrobial agents.

Materials and Methods

Acinetobacter isolates were collected from hospitalized patients with documented nosocomial infections between June 2005 and October 2006. Only one isolate per patient was accepted. Identification of *A. baumannii* strains was made by Gram stain, oxidase test and Vitek 2 GN (bioMerieux/France) system.

Minimum inhibitory concentrations (MICs) were determined by E-test (AB Biodisk, Sweden) according to the manufacturer's recommendations. Mueller-Hinton medium was used for antimicrobial susceptibility tests and the plates were incubated at 5% CO_2 for 24 hours. Antimicrobial agents tested were ampicillin-sulbactam, amikacin, netilmicin, imipenem, ciprofloxacin, cefepime, trimethoprim-sulfamethoxazole, and tigecycline. Evaluation of MIC values was made according to the Clinical and Laboratory Standards Institute (CLSI) guidelines (3). Susceptible break points of ≤2 µg/ml for tigecycline were applied as approved by the United States Food and Drug Administration (FDA) (Tygacil, 2005) and as published in previous studies (4,5). Quality control was performed using *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* 27853 strains.

Results

Overall, 98 *A. baumannii* isolates were collected from the cultures of nosocomially infected patients (Table 1). All of the strains were resistant to more than three antibiotics (multidrug-resistant) and 56 (57.1%) were resistant to imipenem (MIC >32 µg/ml). Forty-four (78.6%) of the imipenem-resistant strains were susceptible to tigecycline (MIC ≤2 µg/ml). Tigecycline was the most active agent tested against *A. baumannii* isolates, followed by netilmicin (Table 2). MIC values of tigecycline were ≤2 µg/ml for 79 (80.6%) of the strains (Table 3).

Table 1. Isolation sites of *Acinetobacter baumannii* strains.

Site of isolation	Number
Wound	34
Blood	33
Deep endotracheal aspirate	15
Urine	12
Sterile body fluids	4

Discussion

Resistance rates are high among the Acinetobacter species isolated from nosocomially infected patients. Recent surveillance studies have shown that the isolates of *A. baumannii* complex are increasingly resistant to cephalosporins, aminoglycosides, fluoroquinolones and carbapenems (6-8). During the past five years, the incidence of nosocomial *A. baumannii* infections appears to have increased, and surveillance studies suggest that highly resistant strains of *A. baumannii* are particularly prevalent among intensive care unit (ICU) patients (1). Management of infections caused by these strains is very difficult, as the strains often display multiple-drug resistance, including carbapenem resistance. In our hospital, most of the Acinetobacter strains are multidrug-resistant and carbapenem resistance rate is high (9,10). Infections with these multidrug-resistant pathogens adversely affect the clinical outcomes and treatment of infections. Thus, new agents to treat these infections are needed.

Tigecycline is a broad-spectrum glycylcycline antimicrobial agent, which acts by binding to the 30S ribosomal subunit. Many other antimicrobial classes, such as aminoglycosides, macrolides, streptogramins and oxazolidinones, act in similar way. Tigecycline, however, overcomes the main types of genetic mechanisms primarily responsible for clinical resistance to these compounds. The glycylcyclines inhibit protein synthesis in wild-type ribosomes, as well as TetM-protected and tet-R ribosomes, and bind five-fold more strongly to the ribosomes than tetracycline and minocycline. It is likely that this enhanced binding is responsible for overcoming

Table 2. Antimicrobial susceptibility to tigecycline and other antibiotics of 98 *Acinetobacter baumannii* strains isolated from nosocomially infected patients.

Antimicrobial agents	MIC (µg/ml)			Susceptibility n (%)
	Range	MIC_{50}	MIC_{90}	
Tigecycline	0.016 - 50	1	4	79 (80.6)
Imipenem	0.016 - >32	>32	>32	42 (42.9)
Ciprofloxacin	0.0125 - >32	>32	>32	14 (14.3)
Netilmicin	0.023 - 64	4	16	77 (78.6)
Amikacin	0.094 - >256	>256	>256	29 (29.6)
Cefepime	1 - >256	24	>256	18 (18.4)
TMP/SMZ	0.016 - >32	>32	>32	25 (25.5)
Ampicillin/sulbactam	0.125 - >256	16	>256	38 (38.8)

TMP/SMZ: Trimethoprim sulfamethoxazole.

Table 3. MIC (µg/ml) values of tigecycline against 98 *Acinetobacter baumannii* strains.

MIC (µg/ml)	Number of isolates (%)
≤2	79 (80.6)
3	7 (7.2)
4	9 (9.2)
16	1 (1)
32	1 (1)
50	1 (1)

the ribosomal protection mechanism of tetracycline resistance (1,8). The most significant characteristic of tigecycline is its activity against resistant Gram-positive bacteria such as penicillin-resistant *Streptococcus pneumoniae,* methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* and many species of multidrug-resistant Gram-negative bacteria, including Acinetobacter species (2).

In the present study, tigecycline was the most active agent against multidrug-resistant *A. baumannii* strains. MIC_{50} and MIC_{90} values were 1 and 4 µg/ml, respectively. Several studies have tested the *in vitro* activity of tigecycline against Acinetobacter species and reported good antimicrobial activity (4,8,11). In a multicenter trial, tigecycline was detected as 8- to 128-fold more active than other agents against Acinetobacter species, and tigecycline MIC_{50} and MIC_{90} results of 0.5 and 1.0 µg/mL were obtained for *A. baumannii* isolates (11). In another study, activity of tigecycline was tested against nosocomial Acinetobacter species from patients hospitalized in the ICU, and it was detected as the most active (MIC_{50}: 1 µg/ml, MIC_{90}: 2 µg/ml, MIC range: 0.06-8 µg/ml) compound (8).

Carbapenem-resistant *A. baumannii* was first reported in 1991. Since that time, several carbapenem-resistant isolates have been reported worldwide (7,12). In 1998, Pandrug-resistant *A. baumannii* was recorded in Taiwan (13). Over the past few years, many of the agents currently used to treat nosocomial infections have failed in the treatment of these resistant strains (14). In the present study, 78.6% of imipenem-resistant isolates were susceptible to tigecycline. In another study, tigecycline exhibited good *in vitro* activity (MIC ≤2 µg/ml) in 42% of imipenem-resistant *A. baumannii* strains (4).

There are some clinical studies showing good efficacy and safety of tigecycline (2,15,16). In one case report, a patient with septic shock due to pan-drug-resistant *A. baumannii* was successfully treated with a combination of antibiotics including tigecycline (17).

In conclusion, tigecycline may have an important role in the treatment of nosocomial infections with multidrug-resistant Acinetobacter isolates, for which there are limited treatment choices available.

References

1. Hawkey P, Finch R. Tigecycline: in-vitro performance as a predictor of clinical efficacy. Clin Microbiol Infect 2007; 13: 354-62.
2. Fraise AP. Tigecycline: the answer to beta-lactam and fluoroquinolone resistance? J Infect 2006; 53: 293-300. Epub 2006 Jul 28.
3. Clinical and Laboratory Standards Institute. Performance antimicrobial susceptibility testing M100-S16. Wayne, Pennsylvania: Clinical and Laboratory Standards Institute; 2006.
4. Insa R, Cercenado E, Goyanes MJ, Morente A, Bouza E. In vitro activity of tigecycline against clinical isolates of Acinetobacter baumannii and Stenotrophomonas maltophilia. J Antimicrob Chemother 2007; 59: 583-5.
5. Pachón-Ibáñez ME, Jiménez-Mejías ME, Pichardo C, Llanos AC, Pachón J. Activity of tigecycline (GAR-936) against Acinetobacter baumannii strains, including those resistant to imipenem. Antimicrob Agents Chemother 2004; 48: 4479-81.
6. Henwood CJ, Gatward T, Warner M, James D, Stockdale MW, Spence RP 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: 479-87.
7. Van Looveren M, Goossens H; ARPAC Steering Group. Antimicrobial resistance of Acinetobacter spp. in Europe. Clin Microbiol Infect 2004; 10: 684-704.
8. Sader HS, Jones RN, Dowzicky MJ, Fritsche TR. Antimicrobial activity of tigecycline tested against nosocomial bacterial pathogens from patients hospitalized in the intensive care unit. Diagn Microbiol Infect Dis 2005; 52: 203-8.
9. Akinci E, Colpan A, Bodur H, Balaban N, Erbay A. Risk factors for ICU-acquired imipenem-resistant Gram-negative bacterial infections. J Hosp Infect 2005; 59: 317-23.
10. Baran G, Erbay A, Bodur H, Onguru P, Akinci E, Balaban N et al. Risk factors for nosocomial imipenem-resistant Acinetobacter baumannii infections. Int J Infect Dis 2007 May 18; [Epub ahead of print].
11. Hoban DJ, Bouchillon SK, Johnson BM, Johnson JL, Dowzicky MJ; Tigecycline Evaluation and Surveillance Trial (TEST Program) Group. In vitro activity of tigecycline against 6792 Gram-negative and Gram-positive clinical isolates from the global Tigecycline Evaluation and Surveillance Trial (TEST Program, 2004). Diagn Microbiol Infect Dis 2005; 52: 215-27.
12. Tognim MC, Andrade SS, Silbert S, Gales AC, Jones RN, Sader HS. Resistance trends of Acinetobacter spp. in Latin America and characterization of international dissemination of multi-drug resistant strains: five-year report of the SENTRY Antimicrobial Surveillance Program. Int J Infect Dis 2004; 8: 284-91.
13. Kuo LC, Teng LJ, Yu CJ, Ho SW, Hsueh PR. Dissemination of a clone of unusual phenotype of pandrug-resistant Acinetobacter baumannii at a university hospital in Taiwan. J Clin Microbiol 2004; 42: 1759-63.
14. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clin Infect Dis 2005; 40: 1333-41.
15. Postier RG, Green SL, Klein SR, Ellis-Grosse EJ, Loh E; Tigecycline 200 Study Group. Results of a multicenter, randomized, open-label efficacy and safety study of two doses of tigecycline for complicated skin and skin-structure infections in hospitalized patients. Clin Ther 2004; 26: 704-14.
16. Oliva ME, Rekha A, Yellin A, Pasternak J, Campos M, Rose GM et al. 301 Study Group. A multicenter trial of the efficacy and safety of tigecycline versus imipenem/cilastatin in patients with complicated intra-abdominal infections. BMC Infect Dis 2005; 5: 88.
17. Taccone FS, Rodriguez-Villalobos H, De Backer D, De Moor V, Deviere J, Vincent JL et al. Successful treatment of septic shock due to pan-resistant Acinetobacter baumannii using combined antimicrobial therapy including tigecycline. Eur J Clin Microbiol Infect Dis 2006; 25: 257-60.