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Brief Original Article

Increasing frequency of *Pseudomonas aeruginosa* infections during tigecycline use

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Abstract

Introduction: The widespread use of tigecycline raises the question of increasing infection rates of *Pseudomonas aeruginosa* (PA) in ICUs which are not affected by this antibiotic.

Objective: The aim of this study was to determine if treatment with tigecycline is a risk factor for PA infection in ICU patients.

Methodology: A retrospective and observational study was conducted at Erciyes University Hospital, Turkey, between 2008 and 2010. The Erciyes University Hospital is a 1300-bed tertiary care facility. The patients included in this study were hospitalized in four adult ICUs. Patients with PA infections (case group) were compared with patients with nosocomial infection other than PA (control group).

Results: A total of 1,167 patients with any nosocomial infections were included in the study. Two hundred and seventy eight (23.8%) of the patients had PA infection during their ICU stay. Fifty nine patients (21.2%) in the case group received tigecycline before developing PA infections, which were found to be significantly more frequent than in the controls ($p < 0.01$). Multivariate analysis showed that risk factors for PA infection were previous tigecycline use (4 times), external ventricular shunt (4.2 times), thoracic drainage catheter (2.5 times) and tracheostomy (1.6 times).

Conclusion: Our results contribute to the need for new studies to determine the safety of tigecycline use, especially for the treatment of critically ill patients. Since tigecycline seems to be an alternative for the treatment of multidrug resistant (MDR) microorganisms, rational use of this antibiotic in ICU patients is essential.

Key words: *Pseudomonas aeruginosa*; tigecycline; infection.

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Introduction

Tigecycline demonstrates potent broad-spectrum in vitro antibacterial activity against clinically important gram-positive and gram-negative aerobic bacteria and anaerobes, with the exception of the intrinsically resistant *Pseudomonas aeruginosa* (PA) [1]. Tigecycline was approved in 2005 for the treatment of complicated intra-abdominal infections, skin and soft tissue infections and for community acquired pneumonia in 2009 [2]. During the same period of time, due to the increase in reported rates of multidrug-resistant (MDR) gram negative bacteria especially among critically ill patients in intensive care units (ICU), the need for new antimicrobial agents has grown. In the search for a solution to the therapeutic limitation of infections due to MDR bacteria, tigecycline became the drug of choice for monotherapy or a component of combined therapies. The widespread use of tigecycline raises the question of increasing infection rates of PA in ICUs which is not affected by this antibiotic. Therefore, we aimed to determine if treatment with tigecycline is a risk factor for PA infection in this study.

Methodology

We performed a retrospective and observational study at Erciyes University Hospital between 2008 and 2010. Erciyes University Hospital is a 1300-bed tertiary care facility. The patients included in this study were hospitalized in four adult ICUs with a 55-bed capacity. The types of ICUs included the medical, surgical, neurosurgical and reanimation. All nosocomial infections defined in these ICUs were recorded by a routine surveillance program in our hospital according to Centers of Disease Control (CDC) criteria [3]. All microorganisms were isolated from clinical samples, and patients with colonization were excluded from the study. Susceptibility tests were carried out according to the Clinical and Laboratory Standards Institute (CLSI) criteria using the disk diffusion method.

The first episode of each infected patient was recorded. Patients with PA infections (case group) were compared with patients with nosocomial infections other than PA (control group). Patients were analyzed according to whether they had received tigecycline before PA infection and also the following data were collected: gender, age, underlying diseases, infections and invasive procedures. Patients with any exposure to tigecycline regardless of the duration of treatment were included in the study.

The statistical analysis was performed using SPSS software version 15.0 (USA). Univariate and multiple binary logistic regression analyses (model: backward Wald) were performed to analyze the effects of variables. Age, respiratory failure and use of central venous catheter were included in the model; however these variables were not significant. Since length of hospital stay before infection may confound the relationship between previous tigecycline use and *Pseudomonas* infection, the results were adjusted for this variable. The level of significance was set at $p < 0.05$ for all tests.

Results

A total of 1,167 patients with nosocomial infections were included in the study. Of these infections, 493 (42.2%) were ventilator-associated pneumonia (VAP), 187 (16.0%) urinary tract infections (UTI), 145 (12.4%) bacteremia, 143 (12.3%) surgical site infections, 59 (5.1%) skin and soft tissue infections and 140 (12.0%) were other nosocomial infections.

The median age of patients was 60 (1-95). Two hundred and seventy eight (23.8%) of the patients had PA infection during their ICU stay. The antibiotic resistance rates of PA strains were 53.3% (144/270) for imipenem, 46.2% (128/277) for cefepime, 44.9 (123/274) for ciprofloxacin, 30.7% (85/192) for amikacin and 28.2 (78/277) for piperacillin/tazobactam. The most frequently isolated microorganisms in the control group were as follows: *Acinetobacter spp*. in 248 patients (27.8%), *E.coli* in 101 patients (11.0%), *Klebsiella spp*. in 100 patients (11.0%), *Staphylococcus spp.* in 53 patients (6.0%), *Enterococcus spp.* in 50 patients (6.0%) *Proteus spp* in 32 patients (3.6%), *S. maltophilia in* 22 patients

Table 1. Univariate and multivariate analysis of risk factors for *Pseudomonas aeruginosa* infections of ICU patients

Variables	No. (%) of patients				Univariate analysis		p	Multivariate analysis		p
	PA infection		Without PA infection		OR	(%95CI)		OR	(95%CI)	
	278	(23.8)	889	(76.2)						
Median age (range)	56.5(1-89)	-	61(1-95)	-	0.992	(0.985-0.998)	0.013			
Female gender	114	(41)	359	(40.4)	1.026	(0.780-1.350)	0.853			
Previous use of tigecycline	59	(21.2)	51	(5.7)	4.427	(2.958-6.625)	0.001	3.992	(2.625-6.071)	**0.001**
Underlying diseases										
Malignancy	28	(10.1)	77	(8.7)	1.181	(0.749-1.862)	0.474			
Hepatic failure	2	(0.7)	8	(0.9)	0.798	(0.168-3.780)	0.776			
Hypertension	44	(15.8)	206	(23.2)	0.623	(0.436-0.892)	0.010	0.686	(0.472-0.996)	**0.048**
Trauma	23	(8.3)	54	(6.1)	1.395	(0.839-2.317)	0.199			
COPD	24	(8.6)	99	(11.1)	0.754	(0.472-1.204)	0.237			
Diabetes mellitus	47	(16.9)	153	(17.2)	0.979	(0.684-1.401)	0.907			
Cardiac insufficiency	13	(4.7)	41	(4.6)	1.015	(0.536-1.922)	0.964			
Renal failure	37	(13.3)	121	(13.6)	0.974	(0.656-1447)	0.898			
Respiratory failure	120	(43.2)	311	(35)	1.412	(1.073-1.857)	0.014			
Use of steroids	23	(8.3)	91	(10.2)	0.791	(0.490-1.277)	0.337			
Invasive devices and procedures										
Surgery	88	(31.7)	244	(27.4)	1.224	(0.914- 1.640)	0.175			
Urinary catheter	250	(89.9)	785	(88.3)	1.183	(0.761-1.838)	0.455			
Mechanical ventilation	239	(86)	688	(77.4)	1.790	(1.233-2.600)	0.002			
Tracheostomy	159	(57.2)	371	(41.8)	1.866	(1.421-2.450)	0.001	1.551	(1.162-2.070)	**0.003**
CVC	201	(72.3)	553	(62.2)	1.586	(1.180-2.132)	0.002			
PVC	95	(34.2)	335	(37.7)	0.854	(0.644-1.133)	0.275			
TDC	26	(9.4)	33	(3.7)	2.676	(1.571-4.560)	0.001	2.543	(1.457-4.441)	**0.001**
Extra ventricular shunt	9	(3.2)	7	(0.8)	4.216	(1.555-11.426)	0.005	4.218	(1.499-11.870)	**0.006**
Colostomy	9	(3.2)	14	(1.6)	2.091	(0.895-4.885)	0.088			

OR: Odds ratio; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CVC: central venous catheter; PVC: peripheral venous catheter, TDC: Thoracic drainage catheter; **Length of hospital stay before infection was considered as a confounding factor, so results were adjusted according to this variable.

(2.5%), *S. marcescens* in 20 patients (2.2%), and other gram-negative rods in 151 patients (17%).

Fifty nine (21.2 %) of the case group patients received tigecycline before PA infection which was found to be significantly more frequent than in the controls ($p < 0.01$). Table 1 shows the univariate analysis of patients' characteristics and of variables associated with PA infection. Multivariate analysis showed that risk of PA infection is higher in situations including previous tigecycline use (4 times), presence of external ventricular shunts (4.2 times), thoracic drainage catheters (2.5 times) and tracheostomy (1.6 times).

Discussion

PA is a frequent cause of serious infections among hospitalized patients and is associated with considerable morbidity and mortality. Several risk factors have been associated with *Pseudomonas* infections [4]. Results in this study are consistent with those in earlier studies in which invasive devices and procedures were mostly associated with PA infections [4,5]. During the last decade, there have been several reports concerning risk factors associated with multidrug-resistant PA [6,7]. Such reports have concluded that the use of anti-pseudomonal antibiotics plays the major role in the emergence of resistant PA infections. On the other hand, a recent study reported that exposure to ertapenem, which has no effect against PA, was found to be associated with resistance [8]. However, molecular tests regarding the type of resistance were not performed. Also in this study, the PA strains isolated from ICU patients were found to be resistant to most of the antibiotics; however, this study does not include data on whether resistance is associated with prior exposure to tigecycline. Similarly, no molecular tests were performed concerning resistance patterns.

Tigecycline, a broad-spectrum antibiotic but ineffective against PA, represents a therapeutic option in the treatment of multidrug-resistant gram-negative infections. The problem arising with widespread use of tigecycline is the emergence of increased rates of PA infection, or infections by other microorganisms with reduced susceptibility to this antibiotic. A recent study indicates that the risk of superinfection rates, particularly on account of PA, increased during tigecycline therapy [9]. The authors reported PA superinfection in 13.7% of 51 patients, a higher rate than previously reported [10,11]. Furthermore, a higher number of new infections and bacterial superinfections after treatment with tigecycline have also been reported in subsequent studies [1,12]. The most striking finding in this study was that prior exposure to tigecycline was also associated with a fourfold increase in the risk of PA infections. This is probably due to the disappearance of tigecycline sensitive pathogens during the treatment with tigecycline and the increase of tigecycline resistant strains such as "PA".

PA is a highly virulent nosocomial pathogen with a broad clinical spectrum of infections. Resistance to multiple classes of antibiotics in this microorganism is also problematic and a source of growing therapeutic challenges. This is a retrospective study performed in a three year period involving a large number of patients. However, the current study is limited by its retrospective design and consequently flawed with insufficient data (duration of tigecycline treatment, initiation time of tigecycline before infection, resistance rates in years).

Conclusions

Recently, based on a meta-analysis of clinical trials, the FDA announced that tigecycline was associated with higher mortality rates, particularly for severe infections [13]. Our results highlight the risks of using tigecycline as monotherapy, especially for the treatment of critically ill patients. Since tigecycline seems to be an alternative for the treatment of MDR gram negative infections, rational use of this antibiotic in ICU patients is essential.

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References

1. Martin-Gandul C, Garcia-Cabrera E, Castillo-Ojeda E, Jimenez-Mejias ME (2012) More about the safety of tigecycline for the treatment of infectious diseases: the role of superinfection rates. J Antimicrob Chemother 67: 1048-1049.
2. Vardakas KZ, Rafailidis PI, Falagas ME (2012) Effectiveness and safety of tigecycline: focus on use for approved indications. Clin Infect Dis 54: 1672-1674.
3. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM (1988) CDC definitions for nosocomial infections, 1988. Am J Infect Control 16: 128-140.
4. Gransden WR, Leibovici L, Eykyn SJ, Pitlik SD, Samra Z, Konisberger H, Drucker M, Phillips I (1995) Risk factors and a clinical index for diagnosis of *Pseudomonas aeruginosa* bacteremia. Clin Microbiol Infect 1: 119-123.

5. Aloush V, Navon-Venezia S, Seigman-Igra Y, Cabili S, Carmeli Y (2006) Multidrug-resistant *Pseudomonas aeruginosa*: risk factors and clinical impact. Antimicrob Agents Chemother 50: 43-48.
6. Paramythiotou E, Lucet JC, Timsit JF, Vanjak D, Paugam-Burtz C, Trouillet JL, Belloc S, Kassis N, Karabinis A, Andremont A (2004) Acquisition of multidrug-resistant *Pseudomonas aeruginosa* in patients in intensive care units: role of antibiotics with antipseudomonal activity. Clin Infect Dis 38: 670-677.
7. Miliani K, L'Heriteau F, Lacave L, Carbonne A, Astagneau P (2011) Imipenem and ciprofloxacin consumption as factors associated with high incidence rates of resistant *Pseudomonas aeruginosa* in hospitals in northern France. J Hosp Infect 77: 343-347.
8. Cohen MJ, Block CS, Moses AE, Nir-Paz R (2014) Exposure to ertapenem is possibly associated with *Pseudomonas aeruginosa* antibiotic resistance. Clin Microbiol Infect 20: O188-196.
9. Garcia-Cabrera E, Jimenez-Mejias ME, Gil Navarro MV, Gomez-Gomez MJ, Ortiz-Leyba C, Cordero E, Pachon J (2010) Superinfection during treatment of nosocomial infections with tigecycline. Eur J Clin Microbiol Infect Dis 29: 867-871.
10. Oliva ME, Rekha A, Yellin A, Pasternak J, Campos M, Rose GM, Babinchak T, Ellis-Grosse EJ, Loh E (2005) A multicenter trial of the efficacy and safety of tigecycline versus imipenem/cilastatin in patients with complicated intra-abdominal infections [Study ID Numbers: 3074A1-301-WW; ClinicalTrials.gov Identifier: NCT00081744]. BMC Infect Dis 5: 88.
11. Sacchidanand S, Penn RL, Embil JM, Campos ME, Curcio D, Ellis-Grosse E, Loh E, Rose G (2005) Efficacy and safety of tigecycline monotherapy compared with vancomycin plus aztreonam in patients with complicated skin and skin structure infections: Results from a phase 3, randomized, double-blind trial. Int J Infect Dis 9: 251-261.
12. Yahav D, Lador A, Paul M, Leibovici L (2011) Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother 66: 1963-1971.
13. Dixit D, Madduri RP, Sharma R (2014) The role of tigecycline in the treatment of infections in light of the new black box warning. Expert Rev Anti Infect Ther 12: 397-400.

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