Original Article

Increased cefepime MIC for enterobacteriacae clinical isolates

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Received: 28 May 2012
Revised: 5 Oct 2012
Accepted: 14 Oct 2012

Abstract

Background: Cefepime was used as empirical treatment in ventilator-associated pneumonia (VAP) induced by gram-negative and gram-positive bacteria. This study aimed to determine the antimicrobial susceptibility pattern of cefepime against microorganism causing VAP in Mazandaran, North of Iran.

Methods: This study was performed on VAP patients diagnosed with clinical pulmonary infection score (CPIS) scores in ICU of two hospitals. For each patient suspected of having VAP, quantitative culture of endotracheal aspiration (QEA) was performed and MIC was determined by micro dilution test. Data were collected and analyzed.

Results: Thirty- five cases of enterobacteriaceae were isolated orderly including E coli 13, P. aeruginosa 11, Enterobacter 7 and K. pneumonia 4 cases. All the isolated E. coli, Enterobacter and Klebsiella, 54.5% of P. aeruginosa isolated were fully resistant to cefepime.

Conclusion: The results of this study show that cefepime is not a reasonable choice for empirical treatment of nosocomial pneumonia and VAP.

Keywords: Cefepime, Enterobacteriacae, MIC, VAP, ICU.

Caspian J Intern Med 2013; 4(2): 654-657

Gram-negative bacteria remain important hospital pathogens, particularly for critically ill patients (1). Klebsiella, Enterobacter species, and Pseudomonas aeruginosa are among the most commonly isolated nosocomial pathogens (2). The mortality rate for patients infected with gram- negative bacteria is 20 to 30% (3). Appropriate antimicrobial treatment is often critical to decrease morbidity and mortality among hospitalized patients with infections (4). Cefepime has a positively charged quaternary ammonium attached to the dihydrothiazone ring, which results in better penetration through the outer membrane of gram-negative bacteria and very active against gram-negative bacilli including Enterobacter, P. aeruginosa, Klebsiella pneumoniae, Serratia, Citrobacter, Proteus mirabilis and less active against Bacillus fragillis (5, 6). Recent studies demonstrate that increase in the prescriptions of third and fourth generations of cephalosporin is a very important risk factor for increasing the resistance of Enterobactericaceae which produce extended spectrum β-lactamase (ESBLs) (7, 8). One pathogen inducing the commonest therapeutic problems in hospitalized patients is gram-negative bacteria.

The mechanism of antibiotic resistance of gram-negative bacteria results mostly from the production of ß-lactamases, enzymes of expanded-substrate profile-ESßL, inactivating all penicillins and most of cephalosporins, and Amp C cephalosporinases (breaking down all penicillins and cephalosporins, third generation ones included) (9, 10). Unfortunately, the resistance of enterobacteriaceae against broad spectrum antibiotics especially cefepime is increasing and difficult in the treatment of nosocomial infections. The aim of this study was to evaluate the sensitivity of clinical isolates of enterobacteriaceae to cefepime.

Methods

This cross sectional analytic study was performed on patients suspected of VAP in ICUs of two university associated hospitals in the province of Mazandaran in Iran from 2009 to 2011. The cases that had a Clinical Pulmonary Infection Score (CPIS) of ≤6 were excluded from this study. After calculating the CPIS score, the cases that were suspected to VAP (CPIS score of more than 6) were further investigated. The CPIS is used to assist in the clinical diagnosis of ventilator-associated pneumonia (VAP) by predicting which patients will benefit from obtaining pulmonary cultures. The use of the CPIS results in fewer missed VAP episodes and can also prevent unnecessary antibiotic administration due to treatment of colonized patients (11).

The micro-organisms in these cases were isolated and their MIC was determined by micro dilution test. This was achieved by obtaining the pulmonary secretion of these cases via intubation and endotracheal aspiration. Subsequently, these collected specimens were sent to clinical microbiology laboratory from October 2009 to March 2011. The specimens submitted to laboratory were cultured in Mueller-Hinton Agar and blood agar. The quantitative positive culture was≥100000 cfu/ml. Microorganism isolates were identified by conventional laboratory approaches, including gram stain and colony morphology (12).

MICs for cefepime were determined by broth micro dilution as recommended by European Committee on Antimicrobial Susceptibility Testing (EUCAST) and MICs were read manually after 24 h incubation. These tests were performed by two experienced laboratory staff and used from antibiotics produced by Merck company. The MIC breakpoints that were used are based on the established criteria by European Committee on Antimicrobial Susceptibility Testing version 1.3 January 2011. Data collection and analysis were done using SPSS version13, and the proportions were recorded.

Results

During the study, 35 cases developed VAP and had positive culture for enterobacteriaceae. The mean age of the patients was 20-75 years. From these, 24(68.6%) cases had underlying diseases including various forms of malignancy, heart disease, diabetes mellitus and trauma. From the 35 isolated enterobacteriaceae, E.coli accounted for about 13 (37.14%) cases, Pseudomonas aeroginosa 11 (31.42%), Enterobacter spp 7 (20%) and Klebsiella pneumonia 4 (11.42%).

All E.coli, Eterobacter and k. pneumonia and 54.54% of P. aeroginosa isolated in this study were cefepime- resistant (Table 1).

Table 1. Cefepime MICs of clinical isolated enterobacteriacae

Sample	E-coli		p.aeroginosa		Enterobacter		k.pneumonia	
	BP	MIC	BP	MIC	BP	MIC	BP	MIC
1	S≤1R>4R:	16	S≤8	4	S≤1	32	S≤1	16
2	100%	16	R>8	32	R>4	32	R>4	32
3		16	R:54.54%	16	R:100%	32	R:100%	16
4		8	I:0.0	0.25		32		16
5		8	S:45.45%	32		32		
6		32		4		16		
7		32		32		32		
8		32		4				
9		16		16				
10		32		16				
11		32		1				
12		16						
13		32						

BP: breakpoint MIC: Minimum Inhibitory Concentration

Discussion

Antimicrobial resistance is a threat to public health worldwide and is associated with higher mortality and morbidity. Despite the extensive knowledge about this problem, drug resistance has continued to emerge, especially in the ICU. With increased application of cefepime, resistance to this antibiotic is increasing and tendency for prescription has decreased. Our study showed high resistance of enterobacteriaceae to cefepime and these findings are worrisome and difficult in the treatment of nosocomial infections in intensive care units. In addition, all of the E. coli isolated in present study was resistant to cefepime. At Concord Hospital, many investigators have recently experienced an upsurge of infections, including bactremias, caused by ESBL-producing strains of *E.* cloacae. They evaluated the in vitro activity of cefepime against these organisms. Extended-spectrum β-lactamase (ESBL)-producing strains of Enterobacteriaceae is a cause of increasing concern worldwide. The results of their investigation have led them to conclude that fourth-generation cephalosporins should not be used for treating serious infections caused by ESBL-producing strains of *E. cloacae* until the outcome of susceptibility testing is known (13). In other study, a total of 142 blood culture isolates from febrile neutropenic patients admitted to one hematology unit were examined, particularly for the detection of cefepime resistance, because cefepime has been used in that unit as initial therapy for febrile neutropenia. Cefepime resistance was seen in 24 (35.3%) of the gram-negative isolates, and had significantly increased in 2007. Approximately 60% of the cefepime-resistant isolates were extended-spectrum β-lactamase (ESBL)-producing organisms. Molecular analysis also showed the predominant emergence of CTX-M types. This result suggests that therapeutic strategies for febrile neutropenia should be modified based on the local antibiotic resistance patterns (14).

Akhabue et al. showed that 8.4% of p. aeroginosa isolates were resistant to cefepime and this occurrence complicates treatment (15). Khorvash et al. showed that 47.1% of isolated bacteria had high level of resistance (MIC ≥256μg/ml) to cefepime (16). Protsenko et al. showed that from October 2003 to December 2004 and from January 2005 to September 2005 had high levels of resistance of Enterobacteriaceae which were 57.5% and 80.5%, respectively (17). Biedenbach et al. evaluated the efficacy of cefepime against E.coli and other gram negative bacilli. They showed fourth–generation cephalosporins (cefepime and cefpirom), and piperacillin/tazobactam were the most active agents tested against gram- negative bacilli (Escherichia coli, Klebsiella spp., Enterobacter) (18).

Early studies about the susceptibility of cefepime showed that the efficacy of this antibiotic was very good and all of the Enterobacteriaceae were susceptible to that. For example study of Chapman and Perry showed that cefepime was an established and generally well tolerated parenteral drug with a broad spectrum of antibacterial activity which when administered twice daily, provided coverage of most of the pathogens that might be causative in pneumonia (19).

This degree of resistance is quite low when compared with prior studies. Regarding E. coli isolates, James et al, reported a >97% susceptibility rate to cefepime (20). Gencer et al. found that 54% of Pseudomonas isolates were sensitive to cefepime (21). In another study, resistance to cefepime was detected only in 30% of P. aeroginosa isolates (22). The limitation of our study was because of the limited cases and further studies with more cases are needed. In conclusion, however, despite a course broad spectrum and good initial efficacy of cefepime on gram positive and gram negative bacteria, because of its expanded use and emerging resistant bacteria, it seems that this antibiotic is not a reasonable choice for the empirical treatment of nosocomial pneumonia especially the ventilator associated type.

Acknowledgments

The authors wish to thank the Research Chancellory of Mazandaran University of Medical Sciences and the laboratory personnel of Ghaemshahr Razi Hospital for their utmost cooperation.

Funding: This project was financially supported by the Research Chancellery of Mazandaran University of Medical Sciences.
Conflict of interest: There was no conflict of interest.

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