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ORIGINAL ARTICLE

Sensitivity pattern of Gram negative bacteria to the new β-lactam/ β-lactamase inhibitor combination: Cefepime/tazobactam

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ABSTRACT

Objectives: Increasing prevalence of carbapenem-resistant Gram negative bacteria has prompted researchers to explore alternative antibiotic options. Different ß-lactam/ß-lactamase inhibitor (BL/BLI) combinations are used in many countries, as a carbapenem saving strategy. The purpose of our study was to evaluate the sensitivity pattern of cefepime/tazobactam combination in comparison to piperacillin/tazobactam, cefoperazone/sulbactam, cefepime and carbapenem agents.

Materials and methods: We conducted retrospective analysis of the sensitivity pattern of Gram negative bacterial isolates in Apollo Speciality Hospital; a 300 bedded, tertiary care Oncology, Neurosurgical and Orthopaedic Centre in South India.

Results: Out of the 1003 Gram negative, non-repetitive isolates collected over a period of one year; 60.5% were sensitive to piperacillin-tazobactam, 46.2% to cefepime, 80.4% to cefepime/tazobactam, 71.3% to cefoperazone-sulbactam, 79.1% to imipenem and 78.2% to meropenem. Addition of tazobactam increased the susceptibility of cefepime from 46.2% to 80.4% in gram negative isolates in general; from 34.4 to 87.9% in *E. coli*, from 42.3 to 81.0% to Klebsiella, from 72.0 to 81.4% in *Pseudomonas* and 17.2-54.5% to *Acinetobacter*.

Conclusion: Cefepime/tazobactam provided a better invitro sensitivity profile than other BL-BLI combinations studied. This in vitro data needs to be confirmed by clinical studies. *J Microbiol Infect Dis 2012; 2(1): 5-8*

Key words: Cefepime/tazobactam, carbapenem sparing strategy, Gram negative resistance, BL-BLI combination.

Yeni β-laktam/β-laktamaz inhibitorü kombinasyonuna Gram negatif bakterilerin duyarlılık paternleri: Sefepim/Tazobaktam

ÖZET

Amaç: Gram negative bakterilerde artan Karbapenem direnci araştırmacıları alternatif antibiyotik seçeneklerini araştırmaya yöneltti. Değişik ß-laktam/ß-laktamaz inhibitor (BL/BLI) kombinasyonları birçok ülkede karbapenemleri koruma stratejisi olarak kullanılmaktadır. Bu çalışmanın amacı sefepim/tazobaktam kombinasyonunun duyarlılık paternlerini araştırmak ve piperasilin/tazobaktam, sefoperazon/sulbaktam, sefepim ve karbapenem ile karşılaştırmaktır.

Gereç ve yöntem: Güney Hindistan'da üçüncü basamak Onkoloji, Nöroşirurji ve Ortopedi merkezi olan Apollo İhtisas Hastanesinde Gram negative bakteri izolatlarının duyarlılık paternlerini inceleyen retrospektif bir araştırma yaptık.

Bulgular: Bir yıllık sürede toplanan 1003 Gram negatif bakteri suşundan % 60,5'i piperasilin/tazobaktama, % 46,2'si sefepime, %80,4'ü sefepime/tazobaktama, %71,3'ü sefoperazon/sulbaktama, %79,1'i imipeneme ve %78,2'si meropeneme duyarlı idi. Tazobaktam eklenmesi ile sefepime olan duyarlılık, tüm gram negatif bakteriler dikkate alındığında %46,2'den %80,4'e; *E. coli*'de %34,4'den %87,9'a, Klebsiella'da %42,3'den %81,0'e, *Pseudomonas*'da %72,0'den %81,4'e ve *Acinetobacter*'de %17'2'den %54,5'e yükseldi.

Sonuç: Sefepim/tazobaktam, çalışmaya alınan diğer BL/BLI kombinasyonlarına göre daha iyi bir invitro duyarlılık profili gösterdi. Bu invitro verilerin klinik çalışmalarla teyit edilmesi gerekmektedir.

Anahtar kelimeler: Sefepim/tazobaktam, karbapenem koruma stratejisi, Gram negatif direnci, BL-BLI kombinasyonu

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INTRODUCTION

Increasing prevalence of extremely drug resistant Gram negative bacteria is a major global concern. The antibiotic pipeline against Gram negative bacteria is dry, with no new promising molecules expected to be marketed in the next couple of years. Extensive usage of carbapenem has resulted in emergence and spread of carbapenem resistant *Enterobacteriaceae, Pseudomonas* and *Acinetobacter*. Beta-lactam/beta-lactamase inhibitor (BL/BLI) combinations like piperacillin-tazobactam and cefoperazone-sulbactam have been extensively used in Indian subcontinent for treating moderately severe sepsis, restricting carbapenem usage to severe sepsis, to a significant extend. Increasing carbapenem resistance has prompted many experts to explore and recommend usage of non carbapenem group of drugs and combinations in many countries.[1] Experts in Indian subcontinent have advocated use of BL-BLI combinations in moderately severe infections due to ESBL producers.[2] Such a carbapenem sparing and restriction strategy may be beneficial in reducing the carbapenem usage and carbapenem resistance rate.[3,4]

Even though piperacillin-tazobactam is available worldwide; cefoperazone-sulbactam, conspicuous by its absence in countries like UK and USA, has gained popularity in many countries, especially India. Coproduction of AmpC and OXA enzymes are widespread in India prompting scientists to search for combinations stable to these enzymes.[5,6] Cefepime/tazobactam is a new promising combination already licensed by the drug controller general of India (DCGI) and increasingly used in Indian hospitals. Combination of a fourth generation cephalosporin with a ßlactamase inhibitor has the theoretical advantage of additional activity against AmpC and possibly OXA enzymes over a third generation cephalosporin-BLI combination.[3] No significant clinical data is available on this drug and limited number of in vitro studies is published till now. A recent study has recorded good invitro activity of cefepime/tazobactam.[7] The aim of our study was to analyse the antibiotic sensitivity pattern of gram negative bacteria to carbapenem and BL-BLI combinations.

MATERIALS AND METHODS

We conducted retrospective analysis of the sensitivity pattern of 1003 Gram negative bacterial isolates in Apollo Speciality Hospital; a 300 bedded, tertiary care Oncology, Neurosurgical and Orthopaedic Centre in South India. Consecutive, non-repetitive Gram negative isolates from various specimens like blood, respiratory secretion, wound swabs and body fluids, from in patients, collected over a span of one year, from July 2010 to June 2011, were analyzed. The culture media used in our study were blood agar (incubated anaerobically if necessary), chocolate agar, CPS3 Chrom agar for urine and MacConkey agar.

Bacterial identification was done using miniAPI strips - Rapid ID32E and ID32GN (bioMerieux). Susceptibility testing was performed by the disc diffusion method by the Kirby- Bauer technique according to CLSI guidelines on Muller Hinton agar.7 The isolates were tested against piperacillin-tazobactam 100/10µg, cefoperazone-sulbactam 75/30 µg, cefepime 30 µg, cefepime/tazobactam 30/10 µg, imipenem 10 µg, meropenem 10 µg and ertapenem 10 µg. While clear cut CLSI guidelines are available for the breakpoint of the most of antibiotics9; guidelines for antibiotics such as cefoperazone-sulbactam and cefepime/tazobactam are not elucidated in the current CLSI guidelines, hence the breakpoint of cefoperazone and cefepime were applied for cefoperazone/sulbactam and cefepime/tazobactam respectively (Table 1). Antibiotic discs were obtained from BD BBL USA, Oxoid UK and HiMedia Lab India. E coli ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used for the quality control.

RESULTS

Out of the 1003 Gram negative non-repetitive isolates, 607 (60.5%) were sensitive to piperacillin-tazobactam, 716 (71.3%) to cefoperazone-sulbactam, and 464 (46.2%) to cefepime, 807 (80.4%) to cefepime/tazobactam, 794 (79.1%) to imipenem and 785 (78.2%) to meropenem (Table 2).

Table 1. Zone Diameter Interpretive Chart - 2009 CLSI (M100 - S19)

Antimicrobial agent	Disc potency	Organisms name	Zone Diameter (mm) Interpretive Standards		
			Resistant	Intermediate	Susceptible
Piperacillin Tazobactam	100/10 µg	*Enterobacteriaceae*, *Acinetobacter*	≤17	18 - 20	≥21
		P. aeruginosa	≤17		≥18
Cefoperazone	75 µg	*Enterobacteriaceae*, *P. aeruginosa*	≤15	16 - 20	≥21
Cefepime	30 µg	*Enterobacteriaceae*, *Acinetobacter P. aeruginosa*	≤14	15 - 17	≥18
Imipenem	10 µg	*Enterobacteriaceae*, *Acinetobacter*, *P. aeruginosa*	≤13	14 - 15	≥16
Meropenem	10 µg	*Enterobacteriaceae*, *Acinetobacter*, *P. aeruginosa*	≤13	14 - 15	≥16
Ertapenem	10 µg	*Enterobacteriaceae*	≤15	16 - 18	≥19

The cefoperazone breakpoints were used to assign S-I-R categories for cefoperazone/sulbactam, since no criteria are currently provided by CLSI for interpreting susceptibility to this drug combination. Cefepime breakpoint was applied for Cefepime/tazobactam.

Table 2. Antimicrobial susceptibility patterns of gram negative bacteria

Microorganisms	PIP/TAZ No (%)	CEF No (%)	CEF/TAZ No (%)	CFP/SUL No (%)	IMP No (%)	MER No (%)	ERT No (%)
Total Gram Negative Bacilli (n=1003)	607 (60.5)	464 (46.2)	807 (80.4)	716 (71.3)	794 (79.1)	785 (78.2)	513 (87.6)
E. coli (n=316,)	183 (57.9)	109 (34.4)	278 (87.9)	254 (80.3)	297 (93.9)	297 (93.9)	286 (90.5)
K. pneumoniae (n=269)	158 (58.7)	114 (42.3)	218 (81.0)	195 (72.4)	249 (92.5)	247 (91.8)	227 (84.3)
P. aeruginosa (n=308)	242 (78.5)	222 (72.0)	251 (81.4)	227 (73.7)	218 (70.7)	213 (69.1)	
A. baumannii (n=110)	24 (21.8)	19 (17.2)	60 (54.5)	40 (36.3)	30 (27.2)	28 (25.4)	

PIP/TAZ=Piperacillin/Tazobactam, CEF=Cefepime, CEF/TAZ=Cefepime/Tazobactam, CFP/SUL=Cefoperazone/Sulbactam, IMP=Imipenem, MER=Meropenem, ERT=Ertapenem

Enterobacteriaceae isolates had 546 (93.3%) susceptibility to imipenem, 544 (92.9%) to meropenem, 513 (87.6%) to ertapenem, and 496 (84.7%) to cefepime/tazobactam. Among the *E. coli* isolates, 278 (87.9%) were sensitive to cefepime/tazobactam, 297 (93.9%) to both imipenem and meropenem and 286 (90.5%) to ertapenem. Cefepime/tazobactam retained sensitivity against 218 (81%) of Klebsiella isolates, while meropenem was active against 247 (91.8%). Cefepime/tazobactam performed well against *Pseudomonas*, being active against 251 (81.4%) isolates, while imipenem was active against 218 (70.7%) and meropenem against 213 (69.1%) of the isolates. Multidrug resistance was most pronounced amongst the *Acinetobacter* with 60 (54.5%) isolates sensitive to cefepime/tazobactam, and only 30 (27.2%) sensitive to imipenem and 28 (25.4%) to meropenem. Susceptibility of the isolates was more pronounced to cefepime/tazobactam than other BL-BLI agents. Addition of tazobactam increased the susceptibility of cefepime from 46.2% to 80.4% to gram negative isolates in general; 34.4-87.9% to *E. coli*, 42.3-81% to Klebsiella, 72-81.4% to *Pseudomonas* and 17.2-54.5% to *Acinetobacter*.

DISCUSSION

Piperacillin-tazobactam was active against half of the *Enterobacteriaceae* isolates while cefepime/tazobactam and cefoperazone-sulbactam were active against majority of these bacteria; cefepime/tazobactam having better coverage than cefoperazone-sulbactam. Susceptibility of *Pseudomonas* to BL/BLI combination was better than to carbapenem. BL-BLI agents performed better than the carbapenem group against *Acinetobacter*; cefepime/tazobactam having a more sensitive pattern than other BL-BLI agents. Tazobactam enhanced the activity of cefepime against both *Enterobacteriaceae* and non-fermenter isolates. One of the main drawbacks of the study is lack of availability of MIC data. Disc susceptibility testing is not the gold standard modality of sensitivity testing and MIC distribution data if available would have increased the credibility of the data. The findings of this in-vitro study need to be confirmed by clinical trials. Our data may encourage other investigators to explore the molecule further.

BL-BLI agents are not traditionally recommended for treating severe infections by ESBL producers.10 Increasing prevalence of ESBL producing organisms resulted in extensive usage of carbapenem group of antibiotics. In countries with good antibiotic policy and antibiotic stewardship, carbapenem usage is restricted in contrary to countries without a functioning antibiotic policy, where uncontrolled usage led to a scenario of alarming carbapenem resistance.[4] BL/BLI combinations may receive more attention in future, as a carbapenem saving strategy. A recent metaanalysis brought out a very interesting conclusion that amoxicillin-clavulanic acid and piperacillin/tazobactam are suitable alternatives to carbapenems for treating patients with bloodstream infections due to ESBLproducing *E. coli*, if sensitive in vitro, especially useful as definitive therapy.[1]

CONCLUSION

Cefepime/tazobactam combination is very promising on the sketch board, predicted to be active against ESBL, AmpC and possibly OXA enzymes and the invitro sensitivity data is in agreement with the prediction. Cefepime/tazobactam combination, if clinical studies yield a similar good result as the laboratory data; may play a significant role as a carbapenem sparing agent.

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