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Antimicrobial Activity of a New Antibiotic Adjuvant Entity (AAE) of Ceftriaxone, Sulbactam and EDTA against Clinical Isolates of Gram Negative Bacteria

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ABSTRACT

Multi drug resistance is increasing worldwide and to curb it judicious use of antimicrobials should be there. Once effective carbapenems and colistin are also facing resistance these days due to irrational use of higher antibiotics. Keeping in view the mounting resistance and paucity of newer antibiotics, a revisiting of an antibiotic combination which can work against these resistant organisms and is a carbapenem sparer is the need of the hour. The fixed dose combinations can be used as an alternative to carbapenems in the treatment of moderate and severe infections caused by gram negative organisms.

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INTRODUCTION

Severe infections caused by multi drug resistant strains (MDR) Gram-negative bacteria are increasing significantly worldwide[1]. The rampant and often incongruous use of broad- spectrum antibiotics have led to the emergence of these MDR pathogens[2]. In Indian hospitals, extended-spectrum beta lactamase (ESBL) and metallo-beta lactamase (MBL) producing gram-negative microbes are the most prevalent organisms responsible for rendering many antibiotics ineffective. As a consequence, very limited therapeutic options like carbapenems and colistin exist[3,4]. Though once effective, at present the carbapenems and colistin are increasingly rendered ineffective due to rising resistance[5,6]. Keeping in view the mounting resistance and paucity of newer antibiotics, a revisiting of an antibiotic combination which can work against these resistant organisms and is a carbapenem sparer is the need of the hour. Few reports have recommended the use of novel ß-lactam/ß-lactamase inhibitor (BL/BLI) combinations like ceftriaxone - Sulbactam (CPT) for restricting usage of carbapenems[7,8]. Likewise, a newer approach to treat the infections caused by these superbugs is being tried by using adjuvants which don't have antimicrobial effect of their own but enhance the antimicrobial activity of the antimicrobial they are combined with[9]. An antibiotic adjuvant entity (AAE) of ceftriaxone, sulbactam and disodium edetate was developed and approved by the Drug Controller General of India (DCGI) and is finding place in the antibiotic armamentarium of Indian hospitals. Sulbactam, a BLI can be effective against various beta lactamase producing microbes. EDTA delivers its antibacterial action through antibiofilm and metal chelating property. It also enhances the penetration of drug by increasing the membrane porosity, which in turn decreased minimum inhibitory concentration (MIC) values of drugs.

MATERIALS AND METHODS

The present study was carried out in a 900-bedded tertiary care teaching hospital in North India to assess the *in vitro* activity of Ceftriaxone + Sulbactam +EDTA (CSE) and to compare it with various other routinely used antibiotics. A total of 145 consecutive, non-duplicate isolates of 42 strains of *Escherichia coli*, 32 of *Klebsiella pneumoniae*, 7 of Enterobacter spp, 6 of *Proteus mirabilis* and 9 of *Citrobacter* spp., 14 of *Pseudomonas aeruginosa* and 35 *Acinetobacter* spp isolated from various clinical specimens, 15 blood, 68 pus, 11 body fluids, 48 respiratory and 03 cerebrospinal fluids between January and December 2018, were included in the study. Ethics committee approval was taken for the

same. These isolates were identified by standard conventional methods and antibiotic susceptibility testing was performed by Kirby Bauer disk diffusion method as per Clinical and Laboratory Standards Institute (CLSI), 2018[10]. Owing to the lack of CLSI interpretive criteria for this AAE, we have used the zone interpretative criteria for ceftriaxone.

RESULTS AND DISCUSSION

The clinical isolates were considered resistant if the zone of inhibition measured by Kirby Bauer's disc diffusion method was found to be less than ≤19mm and sensitive if zone was ≥ 23mm. *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as the controls. In our study, as shown in Table 1, CSE was found to be the most effective drug for all the isolates except *Citrobacter* spp, closely followed by colistin and carbapenems (Imipenem more effective than Meropenem). Also, the third generation cephalosporins were found to be the least effective agents. For the BL-BLI combination PTZ, the susceptibility was seen for only 36% of isolates.

Table No. 1: Comparison of the susceptibility of CSE to various other antibiotics (in percentage)

Organism (no of isolates)	IPM	MER	COL	PTZ	CTN	CSE
Klebsiella pneumoniae [28]	93	43	96	50	7	100
Klebsiella oxytoca [4]	50	25	75	0	0	100
Escherichia coli [42]	81	93	100	45	3	100
Citrobacter koseri [5]	60	20	80	20	0	80
Citrobacter freundii [4]	50	25	75	25	0	50
Enterobacter [7]	98	57	100	57	0	100
Pseudomonas [14]	79	29	100	79	7	100
Acinetobacter [35]	54	46	97	14	0	100
Proteus [6]	67	17	83	33	0	100

Abbreviations: IPM, Imipenem; MER, Meropenem; COL; Colistin; CSE, Ceftriaxone + Sulbactam +EDTA; CTN, Ceftriaxone; PTZ, Piperacillin- Tazobactam.

CONCLUSION

In routine, carbapenems and colistin are widely used nowadays especially in ICU's and high risk wards. Moreover, due to the mounting resistance against carbapenems, there is a dire need to have alternate antimicrobial. *In vitro* susceptibility results of our study suggest that CSE can act as a carbapenem and colistin saving antibiotic as the extensive exposure of carbapenems, emergence of resistance to them and the narrow safety profile of colistin are deterrents to their use. Hence, this new fixed dose combination can be used as an alternative to carbapenem in the treatment of moderate and severe infections caused by gram negative organisms. However, more number of extensive studies are required to establish the breakpoints for susceptible and resistance categories and to establish the safety profile and effective clinical use of this novel combination.

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REFERENCES

1. Paterson DL, Bonomo RA. Extended-spectrum β-lactamases: a clinical update. Clin Microbiol Rev. 2005;18:657-86.
2. Rice LB. The clinical consequences of antimicrobial resistance.Curr Opin Microbiol. 2009;12:476-81.
3. Bush K. Alarming β-lactamase-mediated resistance in multidrug-resistant Enterobacteriaceae. Curr Opin Microbiol.2010;13:558-64.
4. Paterson DL. Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs). Clin Microbiol Infect. 2000;6:460-3.
5. Gupta E, Mohanty S, Sood S, Dhawan B, Das BK, Kapil A. Emerging resistance to carbapenems in a tertiary care hospital in north India. Indian J Med Res. 2006;124:95-8.
6. Varaiya A, Kulkarni N, Kulkarni M, Bhalekar P, Dogra J. Incidence of metallo beta lactamase producing Pseudomonas aeruginosa in ICU patients. Indian J Med Res.2008;127:398-402.
7. Kaur R, Gautam V, Singhal L, Ray P. Antimicrobial activity of cefepime–tazobactam combination tested against clinical isolates of Enterobacteriaceae. J Antibiot. 2014;67:603-4.
8. Ghafur A, Tayade A, Kannaian P. Clinical profile of patients treated with cefepime/tazobactam: A new ß-lactam/ß-lactamase inhibitor combination. J Microbiol Infect Dis. 2012;2:79-86.
9. Sahu M, Sanjith S, Bhalekar P, Keny D. Waging war against extended spectrum Beta lactamase and metallo betalactamase producing pathogens-novel adjuvant antimicrobial agent cse1034-an extended hope. J Clin Diagn Res. 2014;8:DC20-23.
10. Clinical and Laboratory Standards Institute.2018. Performance standards for antimicrobial susceptibility testing. 28th informational supplement. CLSI document M100-S28. Clinical and Laboratory Standards Institute Wayne, PA, USA.

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