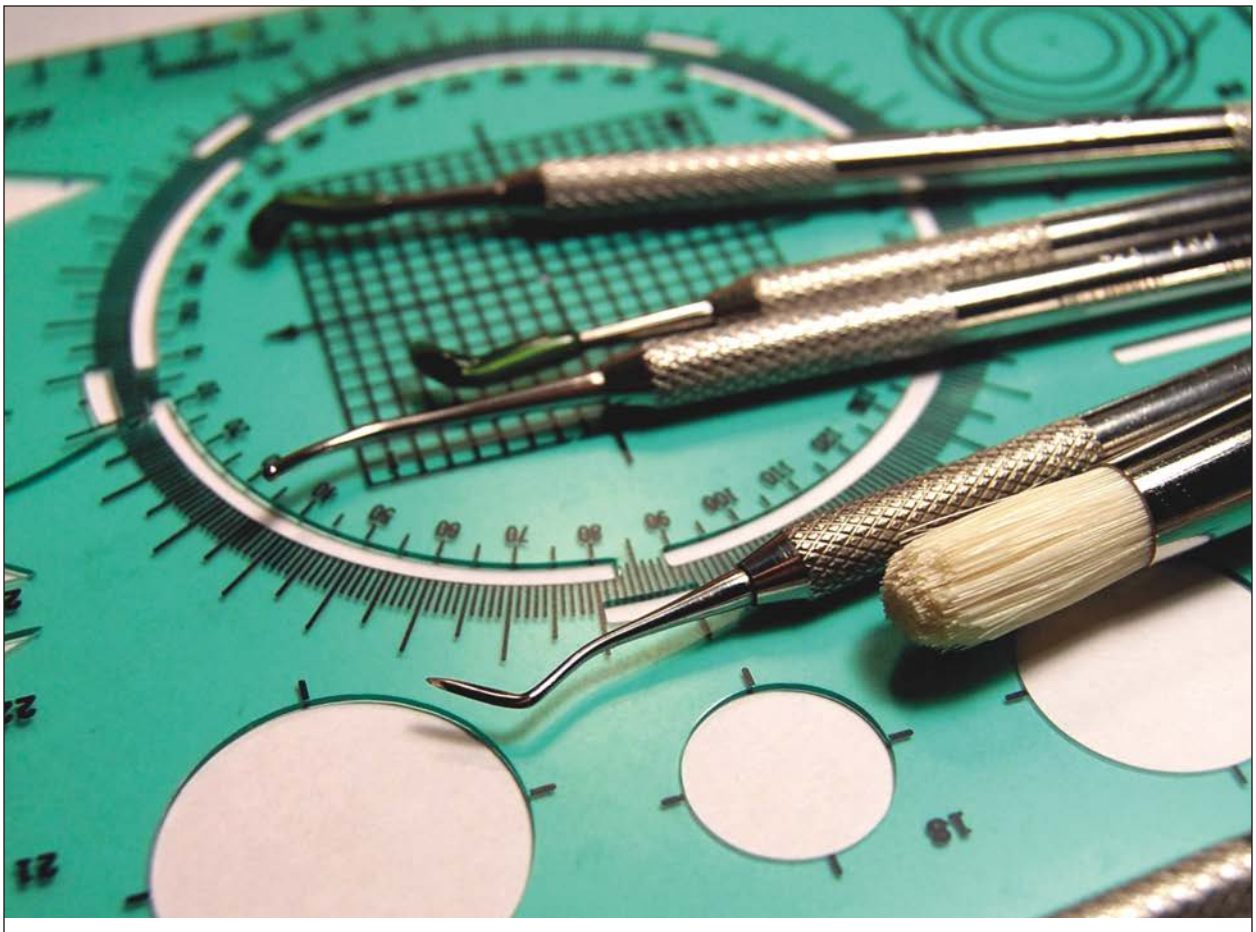

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Evaluation of *in vitro* Efficacy of Cefepime Sulbactam in Combination

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ABSTRACT

In present study, comparative Antibiotic Susceptibility Testing (AST) of combination of cefepime and sulbactam in with cefepime was carried out using susceptibility discs of supime (CPS) and cefepime (CPM). In all organisms under study, lyticzoneproducedbyCPSwasbiggerthanthatof CPM. In case of *P. aeruginosa* more than 48% and *A. baumanii* more than 78% increase in lytic zone size was reported in CPS in comparison to CPM. It is evident that the combination of cefepime and sulbactam has better microbial efficacy when compared with cefepime alone. Use of Supime, the combination of cefepime and sulbactam, in clinical condition, may be preferred over cefepime alone after of successful clinical studies.

Key words: AST, supime, cefepime, sulbactam

INTRODUCTION

Cefepime is a fourth-generation cephalosporin antibiotic which has come into existence in 1994. Cefepime has been proved to have greater efficacy against Gram positive and Gram negative bacteria than third generation cephalosporins. Several pathogenic microorganisms including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Enterobacteriaceae* and resistant *Streptococcus pneumoniae* have been found susceptible to cefepime and therefore, the clinical use of cefepime has increased tremendously in recent past. Cefepime has also been used in the empirical treatment many serious infections including febrile neutropenia. It is also attempted successfully to treat many multiple drug resistant organisms (Chapman and Perry, 2003).

Development of resistance particularly with cephalosporin antibiotics has become a prevalent feature in recent years (Centers for Disease Control and Prevention, 1993, 1997). There are reports of death because of failure of cefepime therapy in infections of Klebsiella pneumoniae (Song *et al.*, 2005). Production of β-lactamase can be one of the probable reasons for development of resistance in pathogenic microorganisms.

Extended-spectrum β-lactamase (ESBL) production is one of the major reasons for development of resistance in organisms (Shay *et al.*, 1995). All β-lactam antibiotics including cefepime are deactivated by these enzymes (Tornieporth *et al.*, 1996).

Sulbactam is an irreversible inhibitor of beta-lactamase, which binds β-lactamase and deactivates the enzyme. This results in protection of activity of antibiotics. Combination of

cephalosporin and β-lactamase inhibitor, such as sulbactam has been one of the present strategies to overcome the resistance mediated by β-lactamase (Shrivastava *et al*., 2009; Gupta *et al*., 2006). Combination therapy using cefepime and sulbactam results in synergistic activity and it is one of the potential means of achieving treatment against infections caused by resistant organisms. Supime, a Fixed Dose Combination (FDC) of cefepime and sulbactam in intended to have more efficacy against organisms which have developed resistance by producing β-lactamase.

Aim of the present study is to evaluate *in vitro* efficacy of cefepime and sulbactam in comparison to cefepime alone so that it can be placed as better alternative after successful clinical evaluation.

MATERIALS AND METHODS

Comparative studies for *in vitro* evaluation of microbial efficacy of supime with cefepime was carried in Venus Medicine Research Centre from January 2009 to March 2009.

Bacterial strains: Bacteria used for this study were pure culture obtained from Microbial Type Collection Centre of Institute of Microbial Technology, Chandigarh, India. Following organisms were procured: *Bacillus subtilis* (MTCC No. -736), *Pseudomonas aeruginosa* (MTCC No. -1688), *Staphylococcus epidermis* (MTCC No. -435), *Citrobacter braaki* (MTCC No. -2690), *Haemophilus parahaemolyticus* (MTCC No. -1776), *Acinetobacter baumanii* (MTCC No. -1425), *Staphylococcus aureus* (MTCC No. -737), *Klebsiella pneumoniae* (MTCC No. -109), *Proteus vulgaris* (MTCC No. -426) and *Escherichia coli* (MTCC No. -1687). Methicillin Resistant *Staphylococcus aureus* (MRSA) used was a clinical isolate obtained from Post Graduate Institute (PGI) of Medical Education and Research, Chandigarh, India.

Antibiotic discs: Discs of FDC of cefepime sulbactam (supime) and cefepime were procured from Hi Media Labs Ltd., India. The susceptibility discs of supime has combination of cefepime and sulbactam (CPS; 30 + 10 μg) and cefepime (CPM; 30 μg).

Media: Mueller-Hinton (MH) agar obtained from Hi Media Lab Ltd., India was used for Antibiotic Susceptibility Test (AST).

Antibiotic susceptibility testing: The comparative Antibiotic Susceptibility Testing (AST) of supime in comparison to cefepime was carried out using susceptibility discs, CPS and CPM, by using method of National Committee for Clinical Laboratory Standards (1997). Twelve discs were used for each test. These susceptibility discs were placed on agar plates pre inoculated with the test organisms. Incubation of plates were done for growth of the organisms and development of lytic zone at 37°C for 24 h. Lytic zone size were measured using zone reader. One-way Analysis of Variance (ANOVA) was used to determine statistical difference between the groups of CPS and CPM. The p-values <0.05 were considered statistically significant.

RESULTS

Staphylococus aureus, *E. coli*, *S. epidermis*, *C. braaki* and *P. vulgaris* have shown statistically significant increase of zone size in case of CPS when compared with CPM. *Pseudomonas aeruginosa*, MRSA, *B. subtilis* and *A. baumanii* have shown very significant ($p<0.01$) increase of zone size. There was no zone reported in the case of *H. parahaemolyticus* for CPM whereas, CPS has shown a zone of 10.3 mm. Non significant increase of zone size was reported in *K. pneumoniae* (Table 1).

Table 1: Comparative results of AST in CPS and CPM

Organism	Drug	Zone of inhibition (mm)
P. aeruginosa	CPS	24.62±2.1
	CPM	16.63±1.2
S. aureus	CPS	29.16±1.6
	CPM	24.47±0.9
K. pneumoniae	CPS	8.98±1.1
	CPM	7.66±1.3
E. coli	CPS	34.87±1.1
	CPM	30.99±0.6
S. epidermis	CPS	29.85±1.5
	CPM	25.21±1.2
MRSA	CPS	29.65±1.2
	CPM	20.90±0.9
B. subtilis	CPS	31.50±2.1
	CPM	18.35±1.8
A. baumanii	CPS	24.11±1.3
	CPM	13.48±1.6
C. braaki	CPS	35.73±1.5
	CPM	31.88±1.1
H. parahaemolyticus	CPS	10.30±0.5
	CPM	-
P. vulgaris	CPS	28.66±1.2
	CPM	25.38±1.3

DISCUSSION

Some bacteria display high-level resistance to β-lactam antibiotics by production of β-lactamase enzyme or production of an extended-spectrum β-lactamase (Bosi *et al.*, 1999; De Gheldre *et al.*, 1997; Galdbart *et al.*, 2000). Cefepime has also been shown to develop resistance particularly because of development of β-lactamase. There are many reports where different combinations of cephalosporins are being used to attain therapeutic significant results (Shrivastava *et al.*, 2009). These antibiotics in presence of β-lactamase inhibitor such as sulbactam rapidly penetrate bacteria and have a high affinity for essential penicillin-binding proteins (Hancock and Bellido, 1992; Kessler *et al.*, 1985). Presence of β-lactamase inhibitor increases efficacy by overcoming resistance of bacteria. However, apart from β-lactamase resistance other mechanism of resistance to cefepime involving changes in the structure of the AmpC cephalosporinase has also been explained. There has been no reports of microbial efficacy analysis of FDC of cefepime and sulbactam in comparison to cefepime alone.

Present study is taken up to determine the efficacy of combination of cefepime and sulbactam in comparison with cefepime alone. The AST results show that *H. parahaemolyticus* used in the study is resistant to cefepime but supime discs has shown efficacy on this organism, which is evident by presence of lytic zone. In all cases, other than *K. pneumoniae*, there has been significant increase of lytic zone size, which is evident of better efficacy of supime. In *K. pneumoniae* there is non significant increase of zone size in supime when compared to cefepime. *In vitro* efficacy of cefepime and sulbactam in comparison to cefepime alone was found to be much higher so that it can be placed as better alternative after successful clinical evaluation.

In conclusion, the combination of cefepime and sulbactam has better microbial efficacy *in vitro* when compared with cefepime alone in large number of pathogenic microorganisms used in this

study. Use of supime, the combination of cefepime and sulbactam, in clinical condition may be preferred over cefepime alone after of successful results of clinical studies.

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