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Comparative Study of Efficacy of Fixed Dose Combination of Ceftriaxone Sulbactam and Ceftriaxone Tazobactam

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In the present study, comparative efficacy of ceftriaxone sulbactam and ceftriaxone tazobactam combinations against *Bacillus subtilis* (MTCC NO. - 736), *Pseudomonas aeruginosa* (MTCC NO. - 1688), *Escherichia coli* (MTCC NO. - 739) and *Klebsiella pneumoniae* (MTCC NO. - 109) was observed. Antibiotic Susceptibility Test (AST) and Minimum Inhibitory Concentration (MIC) of ceftriaxone, sulbactam, tazobactam, ceftriaxone sulbactam combination and ceftriaxone tazobactam combination were analyzed. The percentage effectiveness of ceftriaxone sulbactam and ceftriaxone tazobactam varied for each bacterial species. The difference of effectiveness between the two antibiotics ranged between 0.48 % to 20.65 %. The maximum difference in effectiveness was noticed against *E. coli* (20.65%) and the least was observed against *P. aeruginosa* (0.48%). The MIC value for ceftriaxone sulbactam combination was found to be less as compared to ceftriaxone, sulbactam, tazobactam and ceftriaxone tazobactam combination. In conclusion, the AST and MIC revealed that ceftriaxone sulbactam combination was more effective and can be an excellent therapeutic alternative of ceftriaxone tazobactam and ceftriaxone alone.

Key words: Minimum Inhibitory Concentration (MIC), Antibiotic Susceptibility Test (AST), Ceftriaxone, Sulbactam , Tazobactam.

The third generation cephalosporins were introduced into clinical practice in the early 1980s, and since than, they have served as efficacious and fairly safe agents for the management of many serous infection[1]. The recent appearance of Extended Spectrum β- lactamases (ESBLs), which are capable of conferring resistance to these agents in some Enterobacteriaceae, has compromises the effectiveness if the third generation cephalosporins in clinical practice[2, 3]. However combinations of β-lactam antibiotics and β- lactamase inhibitors seem to has addressed this issue and have proved useful in treating caused by ESBL producing bacteria[4], Therefore a combination of a cephalosporin and β - lactamase inhibitor is used in order to reactivate the antibiotic and to prevent the emergence of resistant bacteria[5,6,7].

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Potential combinations are ceftriaxone, semisynthedtic and third generation cephalosporin and tazobactam a penicillanic acid sulphone derivative which is a potent, irreversible β- lactamase inhibitor and ceftriaxone with sulbactam, a β - lactamase inhibitor[8,9,10,11,12,13]. This in turn has generated considerable interest in combinations of some third generation cephalosporins with β- lactamase inhibitors such as Clavulanic acid, sulbactam or tazobactam, which are capable of inhibiting many of the noval ESBLs[14]. Tazobactam inhibits all β - lactamases inhibited by clavulanic acid, but in addition it also has some activity against chromosomally mediated induced enzymes of *Pseudomonas aeruginosa*. Tazobactam also appears to be a weaker enzyme inducer than other β - lactamase inhibitors. The efficacy of combination of ceftriaxone with tazobactam has been evaluated in certain animal models[15,16] and in certain bacterial species[17].

In combination with a β - lactam antibiotic, these inhibitors have successfully overcome bacterial β - lactam resistance caused by β - lactamase mediated β - lactam hydrolysis. In particular, tazobactam a triazolyl - substituted penicillanic sulfone, has potent inhibitory activity against class A β- lactamases, including some β - lactamases that are resistant to inactivation by Clavulanic acid and sulbactam. Extensive studies have demonstrated that the combination of tazobactam - piperacillin is an effective anti microbiological agent against class A lactamase producing isolates. Tazobactam has been shown to be a more effective β - lactamase inhibitor than sulbactam and furthermore both tazobactam and clavulanic acid are potent inhibitors of not only the conventional spectrum β - lactamases but also of newer enzymes, tazobactam has been shown to be more active than clavulanic acid against OXA - 2 and OXA - 5 enzymes.

The commercially available ceftriaxone sulbactam and ceftriaxone tazobactam combinations are used for common indications. It is required to compare efficacy of these two combinations for better therapeutic importance. Present study was undertaken to compare the *in vitro* efficacy of of ceftriaxone tazobactam and ceftriaxone sulbactam combinations against *B. subtilis, P. aeruginosa, E. coli* and *K. pneumoniae.*

MATERIAL AND METHODS

Bacterial Strains

Following strains obtained from Microbial Type Collection Center of Institute of Microbial Technology, Chandigarh, India were used for the study – *Bacillus subtilis* (MTCC NO. – 736), *Pseudomonas aeruginosa* (MTCC NO-1688), *Escherichia coli* (MTCC NO. – 739) and *Klebsiella pneumoniae* (MTCC-109).

Antimicrobial agents

Ceftriaxone, sulbactam and tazobactam used in study were provided by manufacturer, Venus Remedies Limited, India.

Medium

Mueller- Hinton Broth (MHB) supplemented with calcium (25 mg/l) and Magnesium (1.25 mg/l) was used for MIC and Mueller - Hinton Agar (MHA) was used for Antibacterial Susceptibility Test experiments. Colony counts were determined with MH agar plates.

Efficacy Testing

AST and MIC of ceftriaxone, sulbactam, tazobactam, ceftriaxone sulbactam combination and ceftriaxone tazobactam combination for the *B. subtilis, P. aeruginosa, E. coli* and *K. pneumoniae.* were determined by disc method and broth micro dilution method as per the standard (National Committee for Clinical Laboratory Standards [18]. Overnight MH broth cultures were used to prepare inocula of 10^5 CFU/ml. The MIC was defined as the lowest concentration of antimicrobial agent that prevented turbidity after 24 hours of incubation at 37 °C. Four concentrations of antibiotics named as highest (75 µg), high (50 µg), low (30 µg) and lowest (20 µg) were taken on each disc for AST. Ceftriaxone sulbactam and ceftriaxone tazobactam were taken in the ratio of 2:1 and 8:1 respectively.

RESULTS

The susceptibility test revealed that ceftriaxone sulbactam was more effective as compared to that of ceftriaxone tazobactam. The effectiveness of both the antibiotic combination varied among all the four bacterial species. Both combinations were most effective against

Klebsiella while it was least effective against *P. aeruginosa* in case of ceftriaxone sulbactam while against ceftriaxone tazobactam its was *E. coli.* The percentage effectiveness of ceftriaxone sulbactam and ceftriaxone tazobactam. varied for each bacterial species. The difference of effectiveness between the two antibiotics ranged between 0.48 % to 20.65 %. The maximum difference in effectiveness was noticed against *E. coli* (20.65%) and the least was observed against *P. aeruginosa* (0.48%). (Table 1).

In the *B. subtilis* the MIC results were in ceftriaxone, sulbactam, tazobactam, ceftriaxone - sulbactam and ceftriaxone - tazobactam 2 µg/ml, 8µg/ml, 4µg/ml, 0.50µg/ml and 0.50µg/ml receptively. MIC results were found in *P. aeruginosa* of ceftriaxone, sulbactam, tazobactam, ceftriaxone - sulbactam and ceftriaxone - tazobactam 2 µg/ml, 16µg/ml, 16µg/ml, 0.50µg/ml and 0.50µg/ml receptively. *E. coli* MIC results found in ceftriaxone, sulbactam, tazobactam, ceftriaxone - sulbactam and ceftriaxone - tazobactam 2 µg/ml, 16µg/ml, 16µg/ml, 0.50µg/ml and 1µg/ml receptively. MIC results of *K. pneumoniae* in ceftriaxone, sulbactam, tazobactam, ceftriaxone - sulbactam and ceftriaxone - tazobactam 2 µg/ml, 16µg/ml, 16µg/ml, 0.50µg/ml and 1µg/ml receptively. (Table 2)

DISCUSSION

In recent years many broad spectrum antibiotics have become available, including third generation cephalosporins, carbapenems and fluoroquinolones. Regimens including these antibiotics alone or in various combinations have

Table 1. Comparative AST of ceftriaxone sulbactam combination versus ceftriaxone tazobactam

S. No.	Microorganisms	Concentration	Ceftriaxone Sulbactam Lysis Zone (mm)	Ceftriaxone Tazobactam Lysis Zone (mm)
1	*B. subtilis*	Highest	45.94	44.01
		High	38.78	35.37
		Low	29.62	29.15
		Lowest	21.56	18.50
2	*P. aeruginosa*	Highest	39.47	39.28
		High	33.43	32.44
		Low	28.58	26.42
		Lowest	17.37	11.27
3	*E. coli*	Highest	42.50	33.72
		High	39.63	27.54
		Low	33.26	26.47
		Lowest	26.00	24.55
4	*K. pneumoniae*	Highest	48.06	45.18
		High	36.76	31.84
		Low	25.15	20.91
		Lowest	20.56	14.06

Table 2. Comparative MIC of ceftriaxone sulbactam combination versus ceftriaxone-tazobactam

Organism	Ceftriaxone MIC (mg/L)	Sulbactam MIC (mg/L)	Tazobactam MIC (mg/L)	Ceftriaxone MIC (mg/L)	Ceftriaxone MIC (mg/L)
B. subtilis	2	8	4	0.5	0.5
P. aeruginosa	2	16	16	0.5	0.5
E. coli	2	16	16	0.5	1
K. pneumoniae	2	16	16	0.5	1

been able to considerably lower mortality associated with serious infections; however, the optimal management of fever in "difficult to treat" patients remains controversial, with other factors such as cost effectiveness becoming very important.

Combination therapy with an cephalosporin and a β - lactamase inhibitor has commonly been recommended because this approach provides broad spectrum coverage, bactericidal activity and potential synergistic effects, and minimizes the development of resistance during treatment. To start with mono therapy/combination broad spectrum empiric antibiotics are used, then switching to narrow spectrum specific therapy as guided by microbiological result. Appropriate β-lactam antibiotics are recommended in international and German guidelines for the treatment of mono therapy and combination therapy[19]. Antibiotic combinations consisting of a β - lactam antibiotic and a β - lactamase inhibitor or a β- lactam and an aminoglycoside have frequently produced an increased bactericidal effect in *in vitro* experimental models of aerobic gram negative bacillary infections, which has generally paralleled an increased rate of killing *in vitro*[20, 21].

In our study ceftriaxone alone was found to be less effective against all the bacterial strains while when sulbactam was added to ceftriaxone, the increase in efficacy was noticed . Similar findings were observed with combination of ceftriaxone - tazobactam. MIC values of ceftriaxone sulbactam combination was found lower than ceftriaxone tazobactam combination in organisms under study. AST also showed better efficacy of ceftriaxone - sulbactam than that of ceftriaxone - tazobactam.

In conclusion, combination of ceftriaxone - sulbactam appears to have better *in vitro* bactericidal effect than ceftriaxone - tazobactam and can be explored as better therapeutic alternative.

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