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Original Article

Internal Medicine Section

Antibiotic/Adjuvant Combinations (Ceftriaxone+Sulbactam+Disodium Edetate) to Combat Multi-Drug Resistant Gram Negative Bacterial Infections-A New Therapeutic Strategy

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ABSTRACT

Introduction: In developing countries like India, the topic of particular concern in healthcare settings are gram negative Multi Drug Resistant (MDR) infections, given the limited number of drugs that are currently available as treatment options for these bacterial infections.

Aim: To assess the anti-microbial and clinical efficacy of CSE-1034 in the treatment of MDR gram negative infections.

Materials and Methods: This retrospective study was conducted on 105 patients suffering from gram negative infections and admitted for treatment at tertiary care centre between February 2014-January 2016. The case-sheets of all those patients resistant to initial empirical therapy and shifted to CSE-1034 alone or in combination were evaluated and analysed.

Results: Microbial sensitivity has shown that isolated pathogens from 76 patients were completely sensitive, 24 were intermediately sensitive and 5 were resistant to CSE-1034. The pattern analysis observed in ICU has shown successful clinical response in 66% patients treated with CSE-1034 and 34% were cured with CSE-1034+Colistin therapy. In IPD, 89% were cured with CSE-1034 whereas, 11% were cured with CSE-1034+Colistin therapy. Multivariate analysis revealed no significant association of therapy dose with the hospitalisation status, pathogen involved, gender or infection type.

Conclusion: Empirical use of CSE-1034 can serve as effective alternative to other drugs for the treatment of MDR Gram negative bacterial infections in both IPD and ICU patients.

Keywords: Abdominal infections, Colistin, CSE-1034, Urinary tract infections

INTRODUCTION

The emergence of anti-microbial resistance at a rapid pace is a major crisis faced by medical community at global level [1]. These MDR pathogens prevalent in hospital environment, are observed to have a great impact on patients healthcare cost, morbidity and mortality [2]. Estimates have shown that every year more than 2 million people in US are infected with antibiotic-resistant infections accounting for around 23000 deaths [3]. The situation is even worse in developing countries like India where relatively easy availability and limited financial resources have led to inappropriate and irrational antibiotic consumption and higher level of antibiotic resistance [4].

Gram negative MDR infections which mainly include Urinary Tract Infections (UTI), Lower Respiratory Tract Infections (LRTI), infections of surgical wounds, etc., have emerged as the topic of big concern today in healthcare settings, given the limited number of drugs that are currently available as treatment options for these organisms [2]. Carbapenems is the current drug of choice for management of these infections and has replaced the previously traditionally used cephalosporins due to emergence of resistant strains. However, the alarming increase in the rate of MDR isolates that are carbapenem metabolizers has left us with almost no or few therapeutic options for these resistant strains [5]. This carbapenem resistance is mainly attributed to the ability of the bacteria to produce carbapenamases and Extended-Spectrum Beta-Lactamases (ESBL) [6]. Moreover, the unique structure and the intrinsic impermeability of outer membrane of these gram negative bacteria provide an additional advantage to this group of micro-organisms to acquire highly effective resistance mechanism against various set of drugs [6]. The carbapenemase production is considered a most dangerous resistance mechanism as it lends resistance to several other non-β-lactam antibiotics as well. Thus, the need of the hour is development of new therapeutic strategies to widen the treatment horizon for these dreadful MDR gram negative bacterial infections.

Although, the development of new antibiotics is one of the solutions but unfortunately the rate of new drug development has not kept pace with increasing bacterial antibiotic resistance. One of the latest approach that has emerged as an alternative and cheap option to this problem is the development of potentiators of antibiotic activity known as antibiotic adjuvants. One of the recently approved drugs by Drug Controller General of India (DCGI) is CSE-1034 (Ceftriaxone+sulbactam+adjuvant disodium edetate). The current study is retrospective in nature and aims to analyze the efficacy of CSE-1034 in terms of clinical and microbial parameters in patients with MDR gram negative infections and establish it as potential alternative therapy.

MATERIALS AND METHODS

This retrospective study was conducted on 105 patients suffering from common MDR gram negative bacterial infections including LRTI, UTI, Intra-abdominal Infections (IAI) and admitted in ICU or IPD for clinical treatment at QRG Central Hospital, and Research Centre, Faridabad, Haryana, India, between February 2014 and January 2016. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and to the current norm for observational studies. Informed consent was not needed because of the retrospective nature of study.

The case history sheets of all patients were reviewed and those who fulfilled the inclusion criteria were only considered eligible for the study.

The main criteria for patient inclusion were-

1) The positive and primary diagnosis of gram negative bacterial infections.

2) Received CSE-1034 alone or in combination for a period of ≥3 days.

Patients who died within 72 hours due to multiple complications other than antibiotic failure were excluded from the study.

Information regarding demographic and baseline characters like gender, age, type and source of infection, causative pathogen, co-morbidities, antibiotic therapy, dose and duration for all the patients was retrieved from the case sheets.

The clinical response of the therapy was evaluated in terms of improvement in clinical parameters on daily basis and microbiological evaluation on the day 3 and at the end of treatment. Patients were considered as clinically cured when; a) Afebrile; b) No respiratory symptoms/healed healthy wounds/no dysuria; c) Normal total blood count; d) Normal chest X-ray report.

In-Vitro Microbial Antibiotic-Susceptibility Testing

Kirby-Bauer disk diffusion method/Vitek automated system was used to test the antimicrobial susceptibility of pathogens isolated from patients. Using breakpoints provided by manufacturer, anti-microbial susceptibility for CSE-1034 was performed. Criteria was <21 mm-S, 14-20- I, ≤13-R.

Antibiotic Dosage

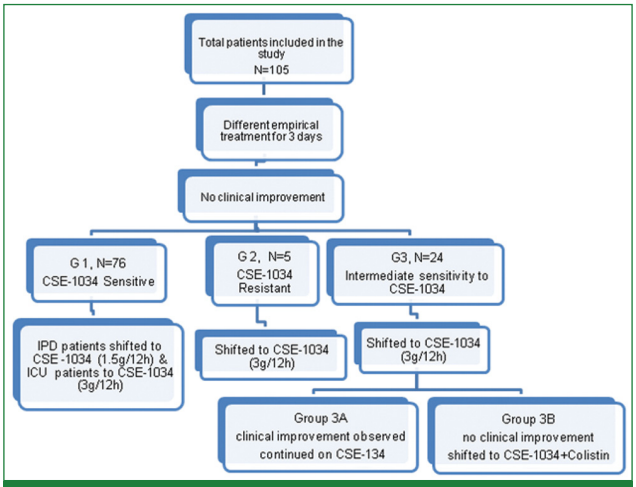
The dosage of CSE-1034 was 1.5 g/12 hours for IPD patients and 3.0 g/12 hours for ICU patients. The dosage of colistin was 9 MIU as loading dose followed by a maintenance dose of 4.5 MIU (BD). For patients having creatinine clearance <10 ml/min, the dose of 1.5 g BD of CSE-1034 was given in ICU patients.

Antibiotic Therapy

At the onset of treatment, the empirical therapies received as per hospital protocol included piperacillin-tazobactam+amikacin for ICU patients and piperacillin-tazobactam for IPD patients.

The analysis of case-sheets revealed that all the patients were resistant to the ongoing antibiotics and had failed to achieve any clinical improvement. All the patients were shifted to CSE-1034 or CSE-1034+Colistin combination therapy based on the microbial sensitivity results.

Depending on further treatment plan, the patients are divided into different groups. Group 1 includes 76 IPD and ICU patients who were CSE-1034-sensitive; Group 2 consists of 5 patients who were CSE-1034-resistant; Group 3 consists of 24 patients who showed an intermediate sensitivity to CSE-1034 [Table/Fig-1].



[Table/Fig-1]: Flowchart elaborating the study design.

STATISTICAL ANALYSIS

All the statistical analysis was performed using Chi-square test. The p-values were two-tailed and a value of <0.05 was considered significant.

RESULTS

A total of 59 ICU and 46 IPD patients were evaluated retrospectively in the current study. The demographic characters of these patients are summarized in [Table/Fig-2]. Classification of patients on the basis of infection diagnosed has shown LRTI as the most predominant infection. Overall, the most frequent cause of these bacterial infections in terms of pathogen were *K. pneumoniae* and *A. baumannii*

No. of Patients	Hospitalisation status	n (%)
Total Patients	ICU	59
	IPD	46
Females	ICU	19
	IPD	14
Males	ICU	40
	IPD	32
Type of Infection		
LRTI	ICU	41 (69.5%)
	IPD	24 (52%)
UTI	ICU	18 (30.5%)
	IPD	19 (41.3%)
Abdominal Infections	ICU	0
	IPD	3 (6.5)
Average age		55.067±13.457

[Table/Fig-2]: Demographic and clinical characteristics of the study group.

in both ICU (35.5%:23.7%) and IPD (34.9%:23.2%) [Table/Fig-3]. The chi-square test of independence has shown a significant co-relation between infection type and the pathogen. However, no significant co-relation with other variables like hospitalisation status, gender was observed [Table/Fig-4]. The most common co-morbidities reported were Chronic Obstructive Pulmonary Disease (COPD), diabetes mellitus followed by heart failure.

Antibiotic Sensitivity Analysis

In vitro microbial testing has shown that 80-85% patients were resistant to amikacin and Pipera-Tazo. Microbial testing against Colistin has shown that 97% (102) were sensitive. The sensitivity reported towards meropenem was 65%. Checking the sensitivity to CSE-1034, it was found that overall 72% (76) were sensitive, 23% (24) had intermediate sensitivity and only 5% (5) were resistant. Coincidentally, all the pathogen samples showing Intermediate sensitivity or resistance towards CSE-1034 were reported meropenem-resistant.

	Family	Pathogen	No of isolates	LRTI	UTI
ICU	Enterobacteriaceae	*K.pneumoniae*	21 (35.5)	13 (31.7%)	8 (44.4%)
		E.coli	9 (15.2)	3 (4.6%)	6 (33.3%)
		E.cloacae	1 (1.8)	1 (4.8%)	0
	Non-Enterobacteriaceae	*A.baumannii*	14 (23.7)	14 (31.7%)	0
		P.aeruginosa	13 (22)	9 (19.5%)	4 (22.2%)
		B.cepaciae	1 (1.8)	1 (4.8%)	0
IPD	Enterobacteriaceae	*K.pneumoniae*	15 (34.9)	11 (46%)	4 (21.1%)
		E.coli	8 (18.6)	0	8 (42.1%)
		E.cloacae	3 (6.9)	1 (4%)	2 (10.5%)
	Non-Enterobacteriaceae	*A.baumannii*	10 (23.2)	9 (37.5%)	1 (5.3%)
		P.aeruginosa	7 (16.3)	3 (12.5%)	4 (21.1%)

[Table/Fig-3]: Percentage prevalence of pathogens isolated from different patients in ICU and IPD.

Variables		Infection Type (LRTI/UTI/ Abdominal infections)	p-value	Hospitalisation status (ICU/IPD)	p-value		
Gender	Male	47/24/1	>0.2068	40/34	>0.4599	29/9	>0.2548
	Female	19/12/2		19/12		44/23	
Dose	1.5g/12 hours	19/16/3	>0.05092	38/38	>0.4918	-	
	3.0g/12 hours	45/21/0		21/8			
Pathogen Type	*K.pneumoniae*	24/12/0	<0.001	21/15	>0.2548	-	
	A.baumannii	23/1/0		14/10			
	P.aeruginosa	12/8/2		13/9			
	E.coli	4/13/1		9/9			
	B.cepaciae	1/0/0		1/0			
	E.cloacae	1/3/0		1/3			
Hospitalisation Status	ICU	41/18/0	>0.05092			-	
	IPD	24/19/3					

[Table/Fig-4]: Co-relation of different variables including infection type, gender, drug dose, therapy type, pathogen and hospitalization status.

Family	CSE-1034 Sensitivity				
	Pathogen	No of Isolates	Sensitive (%)	Interme-diate (%)	Resis-tant (%)
Enteroba-cteriaceae	*K. pneumonia*	36	26(72%)	6(17%)	4(11%)
	E.coli	17	16(94%)	1 (6%)	0
	E. cloacae	4	4(100%)	0	0
Non-enteroba-cteriaceae	*A. baumannii*	23	20(87%)	3(13%)	0
	P. aeruginosa	22	12(54.5%)	9(41%)	1(4.5%)
	B. cepaciae	1	1(100%)	0	0

[Table/Fig-5]: Invitro antibiotic susceptibility testing of CSE-1034 for bacteria isolated from single organism infections.

The highest susceptibility in terms of common isolated pathogens to CSE-1034 was observed in *E. coli* (94%) and *Acinetobacter* sp. (87%) [Table/Fig-5].

Antibiotic Treatment and Outcome

In G1 group, all the 76 (ICU=38; IPD=38) patients who received only CSE-1034 were clinically cured with complete bacteriological eradication within 8±1.98 days. The patients in G2 group (ICU=4; IPD=1) who were shifted to CSE-1034+Colistin combination therapy were also reported completely cured with the additional treatment for 11.5±0.5 days making it to a total of 14-15 days.

In G3 group (ICU=17; IPD=7), all the patients were continued on CSE-1034. On day 3 of 2nd treatment plan, the clinical assessment showed improvement in only 4 (ICU=1; IPD=3) patients whereas, 20 (ICU=16;IPD=4) patients failed to respond and were shifted to CSE-1034 3.0 g dose in combination with Colistin. All the patients were clinically cured after additional 12±0.954 days making therapy to a total of 15-16 days [Table/Fig-1].

Overall, out of 59 ICU patients, successful clinical response was observed in 39 (66%) patients treated with only CSE-1034 and 20 (34%) were cured with CSE-1034+Colistin combination therapy. The pattern analysis in IPD population has shown that 41 (89%) patients were cured with only CSE-1034 whereas 5 (11%) were cured with CSE-1034 and Colistin combination therapy. No significant co-relation of therapy dose with infection type, hospitalization status or gender involved was observed.

DISCUSSION

The rapid increase of MDR organisms has led to a decrease in the efficient way of treating common infectious diseases and ultimately ending up in increased health care expenses, prolonged illness and mortality rate. MDR is a naturally occurring phenomenon and the various options to combat this menace include improved healthcare settings, preventive measures, awareness program, judicious use and prescription of antibiotics, improved knowledge of molecular mechanisms controlling MDR and most importantly continuous search and development of alternate drugs. This study is an attempt to explore a novel drug CSE-1034 as a potential therapeutic option for the treatment of MDR gram negative infections.

The study was conducted on ICU and IPD patients suffering from different gram negative infections including LRTI (62%), UTI (35%) and IAI (3%). The most frequent cause of these nosocomial infections in terms of pathogen was *K. pneumoniae* (35%), *A. baumannii* (22.3%) followed by *P. aeruginosa* (21.3%) and *E.coli* (16.5%). Overall, the pathogens belonging to Enterobacteriaceae accounted for 55% cases and non-Enterobacteriaceae family accounted for 45% cases. Consistent with our results, various studies in the past have demonstrated that Enterobacteriaceae family dominates the gram negative causing bacterial infections [7]. The results are also in line with the previous reports where the main causative agents of Gram negative infections are reported from Enterobacteriaceae family [8].

In-vitro anti-microbial susceptibility testing has shown that 80-85% of patients were resistant to all antibiotics. Compared to this, CSE-1034 sensitivity test has revealed that 64% (38) patients from ICU were completely sensitive, 29% (17) had intermediate sensitivity and 7% (4) were resistant whereas in IPD, 83% (38) were completely sensitive, 15% (7) had intermediate sensitivity and 2% (1) were resistant. As most of the patients were sensitive to this drug in both ICU and IPD definitely gives an edge to this drug over other antibiotics. Various studies in the past have documented that gram negative bacterial infections are gaining resistance to various anti-microbial drugs including the drug of last resort carbapenems [9,10]. One of the approaches to combat this rising antibiotic resistance is the combination of two antibiotics or adjuvant therapy. The potential advantages of these therapies is the increased likelihood of pathogen susceptibility to one of the antibiotic or the synergistic effect of two [11]. The higher susceptibility to CSE-1034 could be likely associated with synergistic effect of ceftriaxone and sulbactam combined with the effect of EDTA. Here, EDTA plays a dual role by inhibiting carbapenemase and by destabilising the outer membrane mediated through metal ion chelation. Similar kind of sensitivity pattern to this novel drug combination has been reported previously also. A multitude of studies from different institutes have documented an enhanced activity of CSE-1034 against various members of Enterobacteriaceae and non-Enterobacteriaceae family [12-14].

All IPD and ICU patients completely sensitive and shifted to CSE-1034, it was found that both clinical and microbiological cure was achieved in all the cases at the end of therapy. Whereas, among rest of the 29 patients showing intermediate sensitivity or complete resistance, four were cured with CSE-1034 (3.0 g/12 hours) and 25 were cured with CSE-1034+Colistin therapy. Thus, overall 75% patients were completely cured with CSE-1034 alone therapy and 25% patients were cured with CSE-1034+Colistin therapy. In support of this outcome, a previous study on dose optimization by Sharma VD et al., [15] has recommended OD dose of CSE-1034 for mild and BD dose for various bacterial infections. This kind of behavior towards drug could be possibly explained through decreased

resistance of pathogen to higher dose mediated via enhanced drug exposure which could be otherwise resistant at lower dose. From these observations, we can also confer that CSE-1034 could be an ideal choice of drug both for IPD and ICU patients at a dose of 1.5 g/12 hours or 3.0 g/12 hours respectively. Furthermore, no significant co-relation observed between drug dose or therapy with hospitalisation status, causative pathogen and gender clears indicates that CSE-1034 is equally effective in all patients irrespective of any of these factors involved.

Multiple lines of evidence have shown that the correct prescription of drugs in empirical therapy leads to improved outcome, reduced mortality, decreased hospitalisation period and financial burden [16,17]. Higher mortality rates are witnessed among hospitalised patients if infecting pathogens are observed to lack sensitivity to the anti-microbial agent prescribed in empirical therapy [18-20]. Evidence suggests that a delayed initiation of effective therapy for patients infected with MDR organisms is more likely to occur and some of this risk can be cut by opting for adjuvant combination antibiotic empirical therapy [21,22]. These observations clearly imply that high sensitivity combined with the synergistic effect of CSE-1034 can make it an ideal option for empirical therapy to improve overall treatment outcome.

Another biggest concern of today is the rise in trend of resistance towards the drug of last resort, carbapenems. One of the best ways to curb this rise is to minimise its intake and spare it for the extreme conditions. Thus, utilising CSE-1034 which is the combination of beta-lactam and beta-lactamase inhibitors with adjuvant in place of carbapenems can help us to reduce their consumption and actually sparing them as last option drugs which can to some extend curb the growing microbial resistance to this class of drugs.

LIMITATION

The drawbacks of this study was its retrospective nature and selective inclusion criteria that can create a slight bias. Therefore, further comparative studies on a larger group of patients need to be done to further validate this study.

CONCLUSION

In conclusion, our data provides a sufficient evidence that CSE-1034 can serve as potential therapeutic option for the treatment of MDR bacterial infections as monotherapy or in combination therapy with other drugs both in IPD and ICU patients.

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