Review Article

A Review Article of Ceftriaxone + Sulbactam + EDTA Treatment in Multi-Drug Resistance Organism

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ABSTRACT

Antibiotic therapy remains gold standard for the management of bacterial infection. The rapid development of multi-drug resistance (MDR) infections has become increasingly evident in recent times, necessitating urgent attention and innovative solutions to combat this issue. Ceftriaxone–Sulbactam–EDTA (CSE) is the first cephalosporin–β-lactamase inhibitor combination with an antibiotic resistance breaker (ARBs)–disodium edetate, recently evaluated in a Phase 3 clinical trial for treatment of adults with complicated urinary tract infections. After phase III clinical trials, this drug got approved in India and thereafter has been marketed for 5 years in India for the treatment of MDR infections. The study goal is to describe the use of Ceftriaxone+ Sulbactam and EDTA Treatment in Multi drug resistance organism.

Keywords: Cetriaxone-Sulbactum-EDTA, MDR, CSE, Cephalosporin, Disodium edentate, Antibiotic resistance breaker, Gram negative organism.

INTRODUCTION

Most healthcare-associated infections in India are caused by multi-drug resistant (MDR) Gram-negative bacteria, thereby posing a therapeutic challenge to treating physicians. With limited treatment options in hand, optimizing antibiotic utilization and exploring alternate options can be a potential way to control this menace[1-5]. Newer therapeutic strategies are needed to be explored to avoid the problems of developing resistance and to save the future of antibiotics. The reports suggested that rational combination therapy of 2 or more antibiotics may be a suitable approach to reduce the frequency of drug resistance in microbes[6].

Ceftriaxone–Sulbactam–EDTA (CSE) is the first cephalosporin–β-lactamase inhibitor combination with an antibiotic resistance breaker–disodium edetate, recently evaluated in a Phase 3 clinical trial for treatment of adults with complicated urinary tract infections[7]. ARBs, sometimes referred as antibiotic adjuvant, are non antibiotic moieties which do not have any antimicrobial activity on its own, but in combination with antibiotics enhance their antimicrobial activity and help overcome resistance barriers[5]. Mechanism of action of this fixed-dose combination is based on the synergism between ceftriaxone (base beta-lactam antibiotic which inhibits bacterial cell wall synthesis), sulbactam (beta-lactamase inhibitor, providing protection against ESBLs) and EDTA (nonantibiotic adjuvant which extends anti-bacterial effect against MBLs and catalyzes resistance breaking mechanisms) respectively[8-10]. Studies have shown that ceftriaxone-sulbactam-EDTA combination is a promising therapeutic option as carbapenem sparer in cases of infections caused by ESBL and MBL producing pathogens[11].

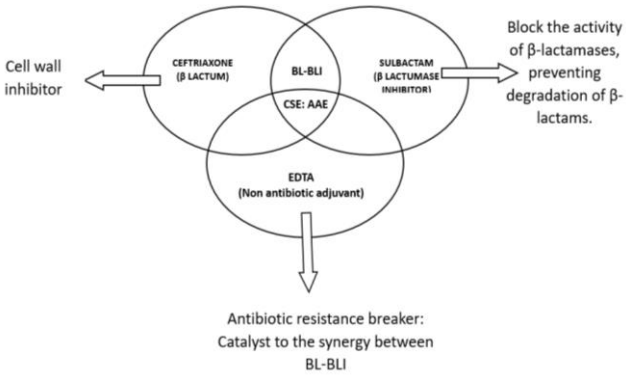

Figure 1[8]

Mechanism of action of CSE has been depicted in the Fig. 1. Various clinical trials of CSE have showed its efficacy towards many MDR micro-organisms as compared to beta lactam-beta lactamase inhibitor combination and carbapenems and have shown that it can act as a potential alternative treatment for reducing the burden on use of last resort antibiotics. After phase III clinical trials, this drug got approved by Indian and thereafter has been marketed in India for the treatment of MDR infections [8]. Combination with Ceftriaxone and Sulbactam enhances the activity of Ceftriaxone-Sulbactam combination and is also reported to break biofilms and inhibit curli formation. EDTA results in reduction in efflux transporter expression, bacterial biofilm eradication (inhibition to form biofilm and making biofilms porous by divalent ion chelation when administered along with antibiotic compounds), and inhibition of curli formation[13].

RESULTS PUBLISHED

CASE: 1

Efficacy of Ceftriaxone+Sulbactam+EDTA Combination for Complicated Urinary Tract Infection Patients: A Retrospective Case Series

Study Findings: The 20 subjects included in this case series study were started CSE-1034 empirically. The decision of starting CSE-1034 empirically was based on the previous hospital exposure and prescription of beta-lactam or beta-lactam/beta-lactam inhibitor (BL/BLI) combination in last 90 days. 90% (18/20) of the patients showed signs of clinical improvement on the 3rd day of CSE-1034 therapy and were continued with same treatment regime. The successful clinical response was observed in all these patients at the end of therapy. The mean treatment duration among these 18 patients was 5.0 days±2.69 (SD). Overall assessment of the clinical response has shown that CSE-1034 monotherapy cured 90% patients alone and 10% patients in combination with levofloxacin. The assessment of microbiological response has shown the complete eradication of the pathogen isolated at the baseline was observed in all 20 patients.[6]

CASE: 2

Ceftriaxone-sulbactam-EDTA Susceptibility Profile of Multi-drug Resistant Gram-negative Bacterial Isolates: Experience from a Tertiary Care Teaching Hospital in Rishikesh, Uttarakhand

Study Findings: Ceftriaxone-sulbactam-EDTA fixed-dose combination seems to be a promising carbapenem sparing therapeutic option in the management of MDR bacterial infections. The percentage antibiotic resistance pattern of the predominant. Gram-negative bacterial isolates, namely Acinetobacter spp., E. coli, Klebsiella spp. and P. aeruginosa, respectively, has been depicted in Table 1. It was observed that 99.1%, 92.7%, 88.6%, and 69.3% of Acinetobacter spp., E. coli, Klebsiellaspp. and P. aeruginosa, respectively, were susceptible to ceftriaxone-sulbactam-EDTA combination disks. While all four isolates of Citrobacter spp. were susceptible to this AAE, the only Proteus spp. isolate obtained in culture was found to be resistant.[1]

CASE: 3

CSE (Ceftriaxone+ Sulbactam+ Disodium Edta): A Possible Solution to the Global Antimicrobial Resistance Pandemic.

Study Findings: A total of 1483 specimens with suspicion of bacterial infection were received in the microbiology laboratory throughout the study period. The cultures came out to be positive in 437 samples, out of which 182 were Gram negative bacteria. In the study majority were urine samples, followed by pus, blood, and others which included body fluids and endotracheal secretion. The most common age group was 20-60 years and females (69/120) outnumbered males though the difference was not statistically significant (p value<0.104). Around 72% specimens were from outpatient department while 23% were inpatients (p value<0.0001). The most common specimen was urine (51.7%), followed by pus (26.7%) and blood (12.5%). Enterobacteriaceae were the most common among the Gram-negative microorganisms (p value<0.0001, 95%CI=0.47-0.9) with E. coli (49%), K. pneumoniae (19%), followed by Pseudomonas spp. (11%) and Acinetobacter spp. (7%)

The susceptibility of E. coli isolates was 85% to amikacin and 76% each to ertapenem and gentamicin. K. pneumoniae isolates were more resistant than other Enterobacteriaceae with 78% susceptibility to amikacin, 73% to ertapenem and 70% to gentamicin. The most resistant among all the Gram-negative bacteria were Acinetobacter spp. with 78% to amikacin and 65% to ertapenem MDR strains were detected in 24% of E. coli isolates, 27% K. pneumoniae, 29% Pseudomonas spp. and 35% of Acinetobacter spp. There is statistically significant difference between sensitivity of beta-lactam (ceftriaxone) & CSE (p value<0.0001) and beta-lactam-beta lactamase inhibitor & CSE (p value<0.0005).[2]

CASE: 4

A Combination Strategy of Ceftriaxone, Sulbactam, and Disodium Edetate for the Treatment of Multi-Drug Resistant (MDR) Septicaemia: A Retrospective, Observational Study in Indian Tertiary Care Hospital.

Study Findings: Total 18 patients of septicaemia were included in the study. The mean age of the patients and average duration of ICU stay was 48.5+12.1 years and 14.5+4.5 days respectively. In addition to positive blood culture, symptoms, and signs compatible with bacteraemia and systemic inflammatory response syndrome (fever or hypothermia, systolic blood pressure, <90 mmHg, tachycardia >90 beats/min and white blood cell count >11 000 cells/mL or, < 4000 cells/mL) were used to evaluate the severity of infection. Among all 18 subjects, 2 (11.1%) subjects revealed moderate infection while 16 (88.9%) subjects displayed severe infection. No subject showed mild infection. Out of 18 patients treated with Elores 3g, 07 (38.8%) subjects completed the treatment within 4-5 days however 8 (44.4%) subjects completed the treatment within 6-7 days. Three (16.6%) subjects completed the treatment in >7 days. Fifteen (83.3%) subjects had complete clinical cure in terms of total relief and no-disease symptoms however 03 (16.6%) subjects revealed treatment failure (TF). With respect to bacteriological response, 15 (83.3%) subjects showed complete bacteriological eradication while 03 (16.6%) subjects showed TF. In general, the settlement or stabilization of clinical signs and symptoms along with settlement of deranged lab parameters with negative culture was treated as cured subjects.

Microbiological data of patients revealed infection of 4 microbes- A. baumannii, E. coli, K. pneumonia and P. aeruginosa distributed in 6, 7, 1 and 4 subjects respectively in all 18 subjects. Results of this study indicate that this

combination therapy (BL/BLI+disodiumedetate) is highly effective against ESBL/MBL producing organisms. The enhanced susceptibility of ceftriaxone, sulbactam and disodium edetate against all 4 microbes is likely to be associated with synergistic activity of this combination. Here presence of disodium edetate enhances permeability of ceftriaxone and sulbactam and thereby enhances activity against ESBL microbes synergistically. Disodium edetate can also chelate the divalent ions required for the activity of MBLs thus deactivating the MBLs which in turn increase the susceptibility of ESBL/MBL producing microbes towards this combination.[12]

CASE: 5

Activity of Ceftriaxone–Sulbactam–EDTA Against Multi-Drug-resistant A. baumannii, P. aeruginosa and Enterobacteriaceae Isolates (WHO Critical Priority Pathogens) Collected from Various Hospitals in India.

Study Findings: Once the genotype data were available, as per the functional classification of β-lactamases into four distinct categories, including ESBL, AmpC, Carbapenemase and MBL. the prevalence was the highest in A. baumannii (78.6%), followed by K. pneumoniae (63%), P. aeruginosa (46.6%) and E. coli (44.1%). CSE showed a high overall susceptibility in ESBL- and MBL-producing bacteria and could provide a useful alternative to carbapenems and colistin in clinical settings.[7]

CASE: 6

Evaluation of a new combination: ceftriaxone – disodium edetate- sulbactam as a broad-spectrum option for multidrug – resistant bacterial infections.

Study Findings: In this study Clinical trials have suggested the clinical and microbiological efficacy of Elores in ESBL – producing showing clinical cure rate of as high as 80.3% as opposed to patients treated with ceftriaxone, which showed a cure rate 30.8%. The microbiological efficacy in terms of bacterial eradication was reported as high as 85.3% in contrast alone (23.1%). Various possible mechanisms have been proposed for enhanced activity of Elores.[3]

CASE: 7

A Retrospective Analysis of the Efficacy of Ceftriaxone-Sulbactam-EDTA Combination for Suspected Biofilm Infections.

Study Findings: Thirty culture-positive adult patients were included in this study. All the patients had received Piperacillin-Tazobactam (Pip-Taz) or Cefaperazone-Sulbactam empirically but none of them responded clinically. Culture susceptibility results available on day 3 have shown that isolates from 40% patients started with Pip-Taz were reported susceptible to Pip-Taz and 45% of patients started with Cefaperazone-Sulbactam were reported susceptible to antibiotic used. 100% of the isolates were susceptible to CSE-1034, 90% to Meropenem and susceptibility to Colistin was 80%. Based on culture susceptibility report and further treatment modifications done, all the patients were switched over to CSE-1034 as 2nd line treatment. A total of 27 patients responded to CSE-1034 and were cured. However, 3 patients who did not respond to CSE-1034 for 48 hours were switched over to Meropenem and reported to be cured.[4]

CONCLUSION

In conclusion, the Combination of Ceftriaxone-sulbactam-EDTA promise as a carbepenam-sparing treatment for MDR gram negative bacterial infections, offering the potential to combat drug resistance while reducing reliance on carbapenam antibiotics with high rates of clinical success and good tolerability.

ABBREVATIONS:

- CSE: Ceftriaxone–Sulbactam–EDTA
- MDR: Multi-Drug Resistant
- ARBs: Antibiotic Resistance Breaker
- EDTA: Ethylenediamine tetra acetic acid
- ESBLs: Extended Spectrum beta-lactamase
- MBLs: Metallo-β-lactamases
- BL/BLI: Beta-Lactam/Beta-Lactam Inhibitor

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