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Original Article

Internal Medicine Section

Post-marketing Safety and Efficacy Evaluation of a Novel Drug CSE-1034: A Drug-use Analysis in Paediatric Patients with Hospital-acquired Pneumonia

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ABSTRACT

Introduction: Hospital-Acquired Pneumonia (HAP) is one of the common and frequently reported nosocomial infections with potential life-threatening complications in paediatric group. One of the drugs approved for treatment of various bacterial infections in all age groups is CSE-1034 (Ceftriaxone+Sulbactam+Disodiumedetate).

Aim: To investigate the efficacy of CSE-1034 in paediatric HAP patients and identify the associated adverse events in real clinical settings.

Materials and Methods: This Post-Marketing Surveillance (PMS) study on CSE-1034 was carried out on 450 paediatric HAP patients across 17 centres in India. Based on age, the patients were divided into three groups including infants, children and adolescents. The following information was recorded-demographic, clinical and microbiological parameters, dosage and treatment duration, concomitant medications and evaluation outcome events of treatment in terms of efficacy and Adverse Events (AEs). The statistical analysis was performed using chi-square test. The p-values were two-tailed and a value of <0.05 was considered statistically significant.

Results: In terms of drug efficacy, 400 patients were cured, 27 showed clinical improvement and 23 were reported as clinical failure. The mean treatment duration varied from 5-7 days. The total number of AEs reported was 55. The common AEs included pain at injection site (3.6%), fever (2.7%), vomiting (2.2%), nausea (1.8%), thromophlebitis (1%), itching (0.4%) and localised pain (0.4%). About 17 AEs were reported in infant group, 18 in children and 20 AEs were reported in adolescent group.

Conclusion: From this PMS study, it can be concluded that CSE-1034 is an effective option for the management of paediatric patients with HAP under routine clinical settings.

Keywords: Adverse events, Gram-negative bacteria, Nosocomial pneumonia

INTRODUCTION

Nosocomial pneumonia, an infection of lung parenchyma that develops in patients after 48 hours of hospital admission, is a common hospital-associated infection in children [1,2]. Despite significant improvement in the quality of patient care, availability of effective drugs and advanced diagnostic facilities, HAP remains one of the prime causes of death and morbidity among hospitalised children [1,3]. The various risk factors for nosocomial infections include mechanical ventilation, under-developed or weaker immune system, underlying illness, antibiotic exposure, invasive diagnostic and therapeutic procedures and hospital environment [4].

Nosocomial pneumonia is often reported to be polymicrobial and gram-negative bacteria form the predominant cause of bacterial HAP particularly in Asia [5-8]. An increasing problem with the bacterial infections is the emergence of multi-drug resistance [9-11]. The increased incidence of infections caused by antibiotic-resistant pathogens contributes to high mortality rate, longer ICU stay and higher treatment costs and constitute a major public threat [9-11]. The selection of appropriate empirical therapy reduces all these factors and maximises the chances of positive outcome. One of the recent approaches to combat antibiotic resistance was the introduction of Antibiotic Adjuvant Entity therapies [12,13]. The synergistic effect of the antibiotic along with adjuvant often justifies its use to combat the growing antibiotic resistance [14,15].

One of the recently DCGI approved novel combination antibiotic to treat bacterial infections in infants and children is CSE-1034, a combination of ceftriaxone and sulbactam along with excipient EDTA [16,17]. Normally, new drugs are launched in the market after regulatory authorities declare that the drug is sufficiently effective and adequately safe after scrutinising the animal and clinical studies done on the product. However, because of the limitations associated with clinical trials inclusion, the information retrieved through them is not enough to predict the safety and efficacy of drug in actual hospital settings. Thus, Post-Marketing Surveillance (PMS) becomes an important part of drug launch to obtain a thorough knowledge about the newly marketed drug and evaluate the drug further in terms of safety and efficacy.

The aim of this observational, open label, multi-centered, prospective, active PMS study was to evaluate safety and efficacy of a novel drug CSE-1034 in paediatric patients with HAP in real clinical settings.

MATERIALS AND METHODS

Study design: This PMS study was conducted on 450 paediatric patients recruited from 17 Indian hospitals in Northern and Southern regions during 2011-2012 treated with CSE-1034.

The study was carried out in accordance with "Guidelines for Clinical Trials on Pharmaceutical Products in India GCP Guidelines" and the ethical principles enunciated in the Declaration of Helsinki. The study was approved by the Independent Ethics Committee Institutional Review Board before commencement. Patients who had given written informed consent were included in the study.

Study population: Subjects of both genders aged between ≤18 years were enrolled in the study. A complete history including signs and symptoms used to make the disease diagnosis, complete physical and laboratory examinations were done prior to enrollment. Inclusion criteria were: a) Fever, leukocytosis or purulent Endotracheal (ET) secretions; b) Radiological features; c) Semi-quantitative culture of the endotracheal aspirate positive for microorganisms.

Subjects who were already diagnosed with pneumonia, recurrence of fever, leukocytosis, radiological worsening and isolation of different microorganism from the ETA after initial improvement was considered as superinfection. Exclusion criteria was, subjects who were allergic to drug and were undergoing treatment with other active drugs. Subjects with a history of hearing loss or with hepatic and renal disorders were also excluded from the study.

Bronchoalveolar Lavage (BAL), mini-BAL or sputum was used for the diagnosis of causative pathogens.

Dosage: The dose of CSE-1034 given to infants and children of up to 12 years of age was 75 mg/kg of body weight (maximum dose of 120 mg/kg body weight in severe infections) and the dose given to children above 12 years of age was 1.5 gm to 3.0 gm every 24 hour or twice daily depending on the severity of infection.

Survey items: Information pertaining to demographics of each patient, the dosage and treatment duration, concomitant drugs, clinical symptoms and bacteriological data of infection and the AEs associated with the treatment were recorded.

Safety: AEs were defined as any untoward medical occurrence taking place during or after treatment with the drug. AEs whether treatment-related or not were decided by the physicians. The seriousness of AEs was determined as per the ICH-E2D (International conference on harmonisation) guidelines and the AEs data were compiled according to the ICH Medical Dictionary for Regulatory Activities [18].

Efficacy: All 450 patients were included in efficacy analysis. Clinical response was defined as improvement in clinical parameters on the day 3 and at the end of treatment plan.

Clinical responses were evaluated on the basis of changes in clinical and microbiological parameters and are categorised as following:

Cure: Resolution of clinical signs and symptoms of original infection, not requiring further anti-bacterial therapy.

Improved: Most, but not all, pre-therapy signs and symptoms subside with no clinically significant worsening or reversal in the course of any of the parameters.

Failure: It includes subjects with persistence of clinical signs and symptoms or worsening in signs and symptoms that required alternative anti-microbial therapy or death.

Bacteriological responses were evaluated on the basis of presence or absence of pathogens in cultures from the collected biological specimens of the subjects.

Various haematological and biochemical investigations including Hb test, ESR, Total Leukocyte Count (TLC), Differential Leukocyte Count (DLC), SGPT, SGOT, ALP, serum creatinine were carried out at the beginning and the end of treatment to evaluate the drug efficacy.

RESULTS

Patient demographic, clinical and microbiological characteristics: The detailed demographic and baseline characteristics of 450 patients enrolled in the current study including number of patients, age, weight, respiratory rate, pulse rate, blood pressure and temperature of the body are given in [Table/Fig-1].

Classification of the patients on the basis of pathogen detected has shown *A. baumannii* to be the most predominant pathogen isolated in 103 patients {Female (F)=39; Male (M)=64} followed by *P. aeruginosa* isolated in 79 (F=28; M=51), *E. coli* in 48 (F=22; M=26), *K. pneumoniae* in 46 (F=20; M=26), *S. pneumoniae* in 36 (F=17; M=19), *S. aureus* in 8 (F=2; M=6). No growth was observed in 130 patients.

Safety assessment: In this study, 55 AEs of various grades were reported in total. The most common AEs were pain at injection site (3.6%), fever (2.7%), vomiting (2.2%), nausea (1.8%) [Table/Fig-2]. The type of AEs reported were similar in all age groups (p>0.05).

Characteristics	Infant (≤2)	Children (>2 to ≤12)	Adolescent (>12 to ≤18)
Total patients (n)	90	164	196
Age (years)	1.4±0.5	6.9±3.2	15.1±1.9
Weight (kg)	9.8±0.6	13±1.6	32.5±10.6
Respiratory rate (/minute)	33.1±5.5	33.1±5.1	33.1±5.2
Pulse rate (/minute)	110.2±21.5	114.8±13.4	102.5±14.2
SBP (mmHg)	92.5±9.2	120.9±4.3	124.9±9.3
DBP (mmHg)	66.2±7.7	81.2±4.3	85.5±12.3
Temperature (ºC)	100.2±1.4	100.2±1.4	100.2±1.3

[Table/Fig-1]: Baseline demographic data of paediatric patients (n=450).
SBP: Systolic blood pressure, DBP: Diastolic blood pressure

AEs	Infants (%) n=90	Children (%) n=164	Adolescents (%) n=196	Grand Total (%) n=450	p-value with respect to age groups	p-value based on the distribution in sub-groups
Total AEs	17 (18.8)	18 (10.9)	20 (10.2)	55 (12.3)	>0.05	
Based on indication						
Pain at injection site	7 (7.7)	4 (2.4)	5 (2.6)	16 (3.6)	>0.05	>0.05
Fever	3 (3.3)	4 (2.4)	5 (2.6)	12 (2.7)	>0.05	
Vomiting	2 (2.2)	3 (1.8)	5 (2.6)	10 (2.2)	>0.05	
Nausea	2 (2.2)	3 (1.8)	3 (1.53)	8 (1.77)	>0.05	
Thrombo-phelibitis	1 (1.1)	2 (1.2)	2 (1.0)	5 (1.1)	>0.05	
Itching	1 (1.1)	1 (0.6)	0	2 (0.44)	>0.05	
Localised pain	1 (1.1)	1 (0.6)	0	2 (0.44)	>0.05	
Based on organ system						
Gastroint-estinal disorders	5 (5.5)	3 (1.8)	4 (2.1)	12 (2.6)	>0.05	<0.05
Dermatologi-caldisorders	11 (12.2)	10 (6.1)	5 (2.5)	26 (5.7)	<0.05	
Nervous disorders	0	5 (3.1)	8 (4.1)	13 (2.8)	>0.05	
Vascular disorders	1 (1.2)	0	3 (1.5)	4 (0.8)	>0.05	
Based on severity						
Mild	16 (17.7)	17 (10.3)	18 (9.2)	51 (11.3)	>0.05	<0.05
Moderate	1 (1.2)	1 (0.6)	2 (1.1)	4 (0.8)	>0.05	
Severe	0	0	0	0		
Based on investigational product (IP) relationship						
Definite	0	0	0	0		
Not related	9 (10)	6 (3.6)	6 (3.1)	21 (4.6)		
Possible	1 (1.2)	2 (1.3)	2 (1.1)	5 (1.2)		
Probable	2 (2.3)	2 (1.3)	3 (1.5)	7 (1.5)		
Unlikely	5 (5.5)	8 (4.8)	9 (4.5)	22 (4.8)		

[Table/Fig-2]: Display of adverse events based on indications, systems and severity (n=55).

Classification on the basis of age has shown no significant difference in the number of AEs reported in different age groups [Table/Fig-2].

Dermatological disorders (26 events, 47%) were the most frequently reported manifestations, followed by gastrointestinal disorders (12 events, 22%), nervous disorders (13 events, 24%) and vascular disorders (4 events, 0.7%). The organ system involved by AEs differed significantly (p<0.05) with maximum number of dermatological and minimum number of vascular disorders. Furthermore, based on age group, no significant difference was observed in AEs belonging to different systems except dermatological disorders. The dermatological manifestations were significantly high (p<0.05) in infant age group and were reported lowest for adolescent age group.

Based on intensity, overall 51 (11.3 %) AEs were mild and 4 (0.8%) were moderate. The rate of severity of AEs were similar ($p<0.05$) in all age groups. Most of the reported AEs were mild and moderate in intensity. No severe AE was reported in any age groups. Based on relationship with IP, 21 AEs were not related, 5 AEs were possible related, 7 were probably related and 22 were unlikely related.

Clinical efficacy: [Table/Fig-3] describes the effectiveness of CSE-1034. All the 450 patients were evaluated for clinical efficacy. In Infant group, 80% were cured completely, 11% showed clinical improvement and 9% were considered as treatment failure. Of the 164 patients in children age group, 90% were cured, 4% had shown clinical improvement and 6% patient were considered as treatment failure. In adolescent age group of 196 patients, 92% patients were cured clinically, 5% showed improvement and 3% were considered as treatment failure.

Clinical response after completion of treatment				
	Cured (%)	Improved (%)	Failure (%)	Total (%)
Total number of patients (n)	400 (89)	27 (6)	23 (5)	450 (100)
Clinical response as per paediatric age group				
Infants	72 (80)	10 (11)	8 (9)	90 (100)
Children	147 (90)	7 (4)	10 (6)	164 (100)
Adolescents	181 (92)	10 (5)	5 (3)	196 (100)

[Table/Fig-3]: Therapeutic outcomes based on age group (n=450).

Depending on the type of pathogen involved, 231/276 (84%) were completely cured, 27/276 (9%) showed clinical improvement and 18/276 (6%) were reported failures in gram-negative group. In gram-positive group, 89% cure was reported and 11% were reported as treatment failure. The per pathogen success rates in terms of complete cure were 88% in *A. baumanii*, 75% in *P. aeruginosa*, 85% in *E.coli*, 87% in *K. pneumoniae*, 89% in *S. pneumoniae* and 88% in *S. aureus* [Table/Fig-4].

Pathogen n (%)	Cured n (%)	Improved n (%)	Failure n (%)
Gram-negative	231/276 (84)	27/276 (10)	18/276 (6)
A. baumanii n=103 (22.8)	91/103 (88)	8/103 (8)	4/103 (4)
P. aeruginosa n=79 (17.5)	59/79 (75)	11/79 (14)	9/79 (11)
E. coli n=48 (10.6)	41/48 (85)	5/48 (10)	2/48 (4)
K. pneumoniae n=46 (10)	40/46 (87)	3 /46 (6.5)	3/46 (6.5)
Gram-positive	39/44 (89)	0	5/44 (11)
S. pneumonia n=36 (8)	32/36 (89)	0	4/36 (11)
S. aureus n=8 (1.7)	7/8 (87.5)	0	1/8 (12.5)
Sterile n=130 (29)	130/130 (100)	0	0

[Table/Fig-4]: Subgroup analysis of therapeutic response based on the type of pathogen.

Treatment duration: The treatment duration varied in clinically improved or cured patients of different paediatric age groups. In Infant age group, the mean treatment duration was 5.5±1.7 days. In children age group, duration was 5.1±1.2 days. In adolescent age group, it was 7.1±3.2 days.

DISCUSSION

One of the most prevalent nosocomial infections in paediatric group is HAP. A proper and appropriate selection of initial empirical therapy plays an important role in reducing the mortality and morbidity associated with HAPs. Moreover, Adverse Drug Reactions (ADRs) represent an important public health problem in the paediatric population [19]. Despite all efforts being made, the morbidity and mortality associated with drug-induced reactions continue to be unacceptably high in this population [20,21]. The aim of this PMS study was to evaluate the safety and efficacy of CSE-1034 for the treatment of HAPs in paediatric population under routine clinical settings.

At the end of study period, it was observed that the drug was well tolerated and 55 AEs ranging in severity from mild to moderate were reported in total in all age groups.

Furthermore, in our study, none of the drug-induced reactions were severe and only 12.7% (7/55) of the AEs were found to have a probable relationship with investigational product (IP). Moreover, the AEs reported were more common in infants (Incidence rate=189) compared to incidence rate of 109 in children and 102 in adolescent age group. Our results correlated well with one of the study, which showed higher incidence of ADRs associated with drugs in patients of age group of 0-2 years [22-24]. Similarly, Priyadharsini R et al., has reported that nearly 60% of the total ADRs reported in their study occurred in patients less than 1 year of age [25].

In our study, the pathogenic agents were identified in 70% of cases. The pathogens most frequently found responsible were *A. baumannii* and *P. aeruginosa* followed equally by *E. coli* and *K. pneumoniae*. These microorganisms are commonly found in most series of nosocomial pneumonias [26]. Various studies have reported aerobic Gram-negative bacilli including Enterobacteriaceae, *Pseudomonas* spp. and *Acinetobacter* spp. as the main causative agents in NP [6,26]. The cure rate for all the pathogens was greater than 85% in each pathogen group, except for *P. aeruginosa* for which the rate was 75%. The overall cumulative cure rate observed in both Gram-positive and Gram-negative pathogen groups was around 87%. The overall mean treatment duration was highest in adolescents followed by children and infants with values equal to 7.1±3.2, 5.1±1.2 and 5.5±1.7 respectively. Although, the eradication rates are at par with the rates achieved in other studies [27,28] employing carbapenems as treatment option for HAP patients which is currently widely used drug to treat Multi-drug resistant infections, the most worrisome part about carbapenems is the continuous rise in the number of Metallo-β-lactamases producing organisms [27]. Carbapenems were once successful therapy for Extended-spectrum beta-lactamases producing organisms and the most effective antimicrobial agents against gram-negative bacterial infections [27]. However, the indiscriminate use of this last resort drug has led to a rise in development of resistance against this class of drug leading to its repeated failure [28,29] and leaving us with few treatment options. MBL producing bacterial strains can hydrolyse a wide range of antibiotics including beta-lactam antibiotics and carbapenems [30].

Collectively, all these reports argue for the identification of alternate therapeutic molecules to prevent this MBL spread and maintain them as the last resort. Since, our novel drug was shown to effectively cure 90-95% in all age groups; it can be an effective alternative for the treatment of bacterial infections. However, further PMS studies with larger number of patients in each paediatric age group need to be conducted for better safety evaluations.

CONCLUSION

Thus, from this study, it can be concluded that the high cure rate and the lesser number of AEs associated with this drug at the study end definitely gives an edge to this drug over others for the treatment of HAPs in paediatric population.

Conflict of interest: Manu Chaudhary, Shiekh Gazalla Ayub, Mohd Amin Mir are the employees of Venus Remedies. All other authors declare that there is no conflict of interest.

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