Journal of Advances in Medicine and Medical Research

27(3): 1-8, 2018; Article no.JAMMR.42695
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Efficacy and Safety of Novel Antibiotic Adjuvant Entity in Hospital Acquired Pneumonia Treatment

Neeraj Kumar Tulara[1*]

[1]Dr. L. H. Hiranandani Hospital, Powai, Mumbai, India.

Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JAMMR/2018/42695
Editor(s):
(1) Zoran Todorovic, Professor, Department of Pharmacology, Faculty of Medicine, University of Belgrade, Serbia.
Reviewers:
(1) Sheikh Mohd Saleem, Government Medical College, India.
(2) Victoire Gadou, Felix-Houphouet-Boigny University, Côte D'Ivoire.
(3) Ruan Carlos Gomes da Silva Centro, Universitário Tabosa de Almeida (Asces-Unita), Brazil.
Complete Peer review History: http://www.sciencedomain.org/review-history/25711

Original Research Article

Received 23rd April 2018
Accepted 6th July 2018
Published 28th July 2018

ABSTRACT

Background and Objective: A multiple number of studies have reported that CSE-1034, an antibiotic adjuvant entity (AAE) of Ceftriaxone-Sulbactam-Ethylenediaminetetraacetic acid (EDTA) is an effective antibiotic for the treatment of various bacterial infections ranging from mild to severe in grade, wherein EDTA acts as antibiotic resistance breaker. The objective of this study was to evaluate the clinical outcome of use of CSE-1034 empirically in hospital acquired pneumonia (HAP) patients. Moreover, as EDTA is widely used anti-coagulant, the other objective included the effect of CSE-1034 on the blood hemostasis.
Methods: This retrospective study was conducted on HAP patients who received CSE-1034 as an empirical treatment to analyze the efficacy and safety of CSE-1034. CSE-1034 therapy was started empirically in all these subjects and continued or discontinued based on culture susceptibility profile and clinical response. The clinical response of the therapy was evaluated in terms of improvement in clinical parameters.
Results: 25 adult patients were included in this study. The most common pathogen isolated was *K. pneumoniae* distantly followed by *E. coli*. Ninety-two percent (23/25) patients who received CSE-1034 empirically were cured with CSE-1034 monotherapy and 8% (2/25) with CSE-1034+Colistin combination therapy. Moreover, no significant alteration in Prothrombin time (PT) and International Normalized Ratio (INR) values were observed in any of the patients during the course of treatment with CSE-1034.

**Corresponding author: E-mail: drntulara@yahoo.com;*

Conclusion: From this study, it is concluded that CSE-1034 alone or in combination with Colistin can serve as an effective and safe option for the treatment of HAP. Moreover, CSE-1034 can be considered as safe drug as no abnormal changes in PT/INR were observed.

Keywords: Ventilator associated pneumonia; prothrombin time; International Normalized Ratio; β-lactam-β-lactam inhibitor.

1. INTRODUCTION

β-lactam antibiotics were one of the most frequently prescribed empirical antimicrobial drugs for the treatment of various bacterial infections. Due to rise in extended spectrum beta-lactamases (ESBL) producing strains that hydrolyze most of the beta-lactam antibiotics, they were later replaced by β-lactam-β-lactam inhibitor (BL-BLI) combinations [1,2]. Although BL-BLI combinations played a vital role in the management of infections caused by ESBL producing organisms, a considerable increase in BL-BLI resistance cases has been reported worldwide [3,4]. To combat this growing antimicrobial resistance, antibiotic adjuvant therapies are widely practiced and are considered one of optimum approach [5,6]. A novel antibiotic adjuvant entity (AAE), combination of Ceftriaxone, Sulbactam and EDTA has been recently used as an alternative to fight the drug resistance. A multitude of studies has reported that CSE-1034 is an effective antibiotic for the treatment of various multi-drug resistant (MDR) bacterial infections [7,8].

Pneumonia is classified as HAP if it is not present at admission time and occurs 48 h or more after hospital admission. HAP accounts for around 15% of the hospital-acquired infections (HAIs) and occurs at a rate between 5 to 15% cases per 1000 hospital admissions [9]. Intubation and mechanical ventilation are the most important risk factors for HAP specifically called as ventilator-associated pneumonia (VAP). The incidence of VAP is 6-21 fold high in mechanically ventilated patients, rendering VAP as the most common HAIs in ICU patients [9]. Various drug treatments particularly beta-lactam antibiotics including Cefamandole, Cefmenoxime, Cefmetazole, Cefoperazone and Latamoxef are reported to be associated with defects in hemostatic mechanisms and thus precipitating bleeding [10,11]. The aim of this study was to evaluate the co-relation of microbial susceptibility pattern of CSE-1034 with clinical outcome in addition to evaluate the effect of CSE-1034 on hemostasis of patients. This study is based on a series of patients suffering from HAP who have been treated with CSE-1034.

2. MATERIALS AND METHODS

2.1 Study Population

This retrospective study was conducted on adult patients (age ≥18 years) suffering from HAP and admitted to the hospital for treatment between June 2016 to December 2016. The criteria for patient inclusion were 1) The primary diagnosis of HAP including ventilator associated pneumonia (VAP) based on various lab parameters and relevant signs and symptoms 2) Received CSE-1034 as the empiric treatment 3) Received CSE-1034 at least for a period of ≥3 days 4) PT/INR was done. Exclusion criteria (1) Patients who received CSE-1034 for less than 3 days (2) Received CSE-1034 but PT/INR was not done.

In our hospital, *in-vitro* antimicrobial susceptibility testing (AST) on 250 microbial isolates was done. Based on a good susceptibility pattern, CSE-1034 was started as empiric therapy in patients with healthcare-associated infections including hospital-acquired pneumonia (HAP).

2.2 Patient Analysis, Antibiotic Usage, and Outcomes

Information regarding demographic and clinical characters like gender, age, type and source of infection, causative pathogen, co-morbidities, antibiotic therapy, dose and duration, laboratory investigations done for all the patients were retrieved from case history sheets.

Patients had undergone various hematological and biochemical investigations including blood count, Liver function test (LFT), urine analysis.

Specimens of sputum or pleural fluid culture, endotracheal (ET) secretions were used for the isolation of baseline pathogens.

In vitro microbial susceptibility testing of the isolated pathogen was done using Kirby-Bauer disk diffusion method and the results were interpreted as per the interpretation criteria of the Clinical and Laboratory Standards Institute (CLSI) standards (EUCAST, 2016). Using breakpoints provided by manufacturer, AST for CSE-1034 was performed. Criteria was ≥ 21 mm-S, 14-20-I, ≤13-R.

The dose of AAE used was 1.5 g or 3.0 g every 12 h.

The clinical response of the therapy was evaluated in terms of improvement in clinical parameters on daily basis and at the end of treatment.

2.3 Diagnosis Criteria

The patients included in this study were ICU patients diagnosed with HAP including VAP.

Symptoms of HAP included fever (>100.4 F); leukocytosis (>12,000 WBC/mL); cough with purulent ET secretions; abnormal chest radiographs showing lobar or multi-lobar infiltrates. Other symptoms include new-onset of worsening cough, dyspnea/tachycardia, rales, bronchial breath sounds or egophony.

Symptoms of VAP in mechanically ventilated patients include fever (>100.4 F), leukocytosis (>12,000 WBC/mL), chills, rigor, increased respiratory rate or heart rate or changes in respiratory parameters like increase in purulent secretions/sputum or worsening hypoxemia, abnormal chest radiographs.

Here the term first line antibiotic therapy is defined as the regime started at the beginning after the admission to the hospital.

Second-line antibiotic therapy is defined as the addition of one or more antibiotics to the initial regime or a complete or partial replacement of the initial antibiotic with another parenteral antibiotic regime depending on AST results.

3. RESULTS

3.1 Subjects and Their Baseline Characteristics

A total of 75 patients suffering from various nosocomial infections and who received CSE-1034 as empirical treatment were screened. 25 patients meeting our study entrance criteria were included in this study. The analysis of APACHE II score had shown a score of <15 in majority patients. For other demographic parameters like age, weight, height, respiration rate, pulse rate, SBP, DBP, temperature, refer to Table 1.

VAP cases were more compared to HAP. Diabetes mellitus was the most common co-morbidity followed by hypertension, chronic kidney disease, cardiovascular diseases and hepatic disorders (Table 1). *K. pneumoniae* was the predominant Gram negative pathogen

Table 1. Demographic and baseline details of the study subjects (n=25)

Characteristics		(n=25)
Gender	Male, n	14 (56%)
	Female, n	11 (44%)
Age (year)	Mean±SD	74±18.55
Height (cm)	Mean±SD	170±5.88
Weight (kg)	Mean±SD	79±14.77
Temperature (˚F)	Mean±SD	101±1.81
BP (mm of Hg)	Systolic (Mean±SD)	130±14.68
	Diastolic (Mean±SD)	80±8.30
Pulse (beats/min)	Mean±SD	100±16.05
Respiratory rate (/min)	Mean±SD	24±9.79
Diagnosis n (%)	VAP	16 (64%)
	HAP	9 (36%)
Apache II score	<15	18 (72%)
	≥15	7 (28%)
Co-morbidities n (%)	DM	16 (64%)
	Hypertension	10 (40%)
	Chronic kidney disease	08 (32%)
	Cardiovascular diseases	07 (28%)
	Hepatic disorders	03 (12%)

Table 2. *In-vitro* antibiotic susceptibility testing of the pathogen isolated to various antibiotics

Antibiotic	*K. pnuemoniae* (14)		*A. baumannii* (7)		*E. coli* (7)	
	Resistant N (%)	Sensitive N (%)	Resistant N (%)	Sensitive N (%)	Resistant N (%)	Sensitive N (%)
Pip-Taz	13 (92.8)	1 (7.14)	5 (80)	2 (20)	4 (100)	0
Meropenem	2 (14.28)	12 (85.71)	0	7 (100)	2 (50)	2 (50)
CSE-1034	1 (7.14)	13 (92.85)	0	7 (100)	1 (25)	3 (75)
Colistin	0	14 (100)	0	7 (100)	0	4 (100)

Table 3. Display of outcomes based on the type of infection and pathogen

	CSE-1034	CSE-1034+Colistin
Total		
Clinical cure	23/23 (100)	2/2 (100)
Clinical failure	0	0
Bacteriological eradication	23/23 (100)	2/2 (100)
Based on infection		
VAP	15/16 (93.75)	1/16 (6.25)
HAP	8/9 (88.9)	1/9(11.1)

Table 4. Hematology parameters (mean) of all the treatment groups before and after treatment

Laboratory parameters	Screening	Completion	p-value
Hb (g %)	13.02±1.69	12.19±1.32	0.0589
E.S.R (mm/h)	41.2±17.16	39.02±10.66	0.592
T.L.C (/mm3)	11231.2±3864.01	8839.21±2761.01	0.015
Lymphocytes (%)	12.46±6.01	21.87±7.25	0.0001
Blood Urea nitrogen (%)	18.5±9.77	12.4±8.02	0.0197
S. Creatinine (mg/dl)	1.26±0.46	0.83±0.39	0.0008
S.G.P.T (U/L)	30.11±8.74	19.33±9.11	0.0001
S.G.O.T (U/L)	41.03±11.12	21.61±7.21	0.0001
A.L.P (U/L)	139.75±46.17	107.24±13.21	0.0014
INR	0.9±0.11	0.95±0.09	0.085
PT	12.0±1.24	11.7±1.88	0.508

isolated distantly followed by *E. coli* and *A. baumannii*. For further details, refer to Table 2.

3.2 Antibiotic Sensitivity Analysis

In vitro AST of Piperacillin-Tazobactam (Pip-Taz), Meropenem and CSE-1034 are presented in Table 2. Culture sensitivity analysis has shown that pathogens isolated from 92% (23/25) patients were completely sensitive to AAE, 84% (21/25) to Meropenem and 12% (3/25) to Pip-Taz. The sensitivity to Colistin was 100%. Two patients were reported resistant to Pip-Taz, CSE-1034 and Meropenem and only Colistin sensitive. Although 21 patients showed both Meropenem and CSE-1034 sensitivity, but based on antibiotic stewardship policy of our hospital CSE-1034 was preferred as empirical choice and reserve Meropenem for CSE-1034 non-sensitive cases in need.

3.3 Antibiotic Outcome

All the 25 subjects included in this study were started with CSE-1034 empirically as per Intensivist's decision. The clinical responses observed in all the patients were in line with the microbial susceptibility results. All the (23/25) patients who were culture sensitive and received

CSE-1034 empirically were reported to respond clinically. The mean treatment duration among these 23 patients was 10.0 days±1.86 (SD). 2 patients who were reported to be both CSE-1034 and Meropenem resistant received Colistin as an add-on to the ongoing CSE-1034 therapy and were also reported to be cured. The mean treatment duration in patients cured with CSE-1034 and Colistin combination therapy was 13 days±1.4 (SD).

Overall assessment of the clinical response has shown that CSE-1034 monotherapy cured 92% of the patients and 8% of the patients were cured with CSE-1034 and Colistin combination therapy. For other details, refer to Table 3.

3.4 Pro-thrombin Time

In all 25 patients analyzed, PT/INR was performed on alternate days based on underlying co-morbidities and undergoing different procedures including urological, tracheostomy, incision and drainage, etc.

For our study purpose, we have calculated the mean of values obtained at the beginning and end of treatment. The mean PT/INR values for all the patients along with other laboratory investigations are shown in Table 4. None of the patients had reported any significant difference in PT/INR values either at the beginning or at the end of treatment.

3.5 Statistical Analysis

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

4. DISCUSSION

EDTA has been reported as antibiotic resistance breaker (ARB) with strong catalytic action thereby breaking various resistance mechanisms due to chelation and has emerged as the potentiator of the activity of existing antimicrobial agents. Various studies have demonstrated numerous antimicrobial and anti-biofilm properties associated with EDTA [12,13]. Sharma et al. [13] has reported that EDTA enhances the use of a photodynamic agent against *S. aureus* biofilms. Yoshizumi et al. [14] reported that Ca-EDTA enhanced the activity of Imipenem in sepsis mouse model. Similarly, Manu et al. [15] have demonstrated that EDTA when used in combination with Ceftriaxone and Sulbactam enhances the activity of the Ceftriaxone/Sulbactam combination, with EDTA reported to sequester Mg^{2+}, Ca^{2+} and Zn^{2+} ions required for functioning of the bacteria to exhibit various resistance mechanisms like efflux pump, porin channels etc [16,17]. Moreover, EDTA as a component of CSE-1034 is also reported to break biofilms and inhibit curli formation [18].

In this study, a high microbial susceptibility towards CSE-1034 (92.85%) reported was in concordance with the clinical response in patients treated with CSE-1034 (92% with monotherapy and 8% with Colistin combination therapy). Various papers have demonstrated that Ceftriaxone-Sulbactam-EDTA combination is an effective treatment for ICU bacterial infections including MDR ones [19,20]. The higher susceptibility of CSE-1034 could likely be attributed to synergistic activity of Ceftriaxone plus Sulbactam plus EDTA. Other than the combined effect of Ceftriaxone-Sulbactam, a non-antibiotic adjuvant, EDTA mediates various antimicrobial effects by sequestering the metal ions required for executing various resistance mechanisms. EDTA chelates divalent metal ions located in the outer membrane causing destabilization of outer membrane, de-activates carbapenemases by chelating Zn^{2+} ions required for its functioning and chelates Mg^{2+} ions required for the activity of DNA relaxases in conjugation process resulting in the inhibition of conjugal spreading of resistant genes from one bacteria to another [15].

In our study, we observed a little higher susceptibility to CSE-1034 compared to Meropenem. A good number of previous studies have reported that the microbial sensitivity of CSE-1034 is at par with Meropenem or even better in some cases. Bhatia et al. [21] have reported overall sensitivity of 90% to CSE-1034 against 74% to Meropenem for various gram-negative isolates. Almost similar kind of pattern has been reported by Verma et al. [22] who showed that of 64 bacterial isolates from patients with mono-microbial infections, 78.13% showed susceptibility towards carbapenem and all 64 (100%) isolates showed susceptibility towards CSE-1034. Moreover in line with our results, the antimicrobial resistance data in India has shown that resistance against Pip-Taz has risen to 65-70% [23]. As 92.85% of the patients were sensitive to CSE-1034 and were effectively cured

with CSE-1034 alone, thus CSE-1034 can be an effective option as empirical therapy for the treatment of HAP patients. Although 85.71% of the isolates were sensitive to Meropenem also, however the over use of carbapenems has lately led to rise in carbapenemase producing bacterial strains which calls for the need to follow strict antibiotic restriction policies, and therefore to avoid the excessive use of carbapenems and following antibiotic stewardship policy we preferred CSE-1034, a lesser grade drug. No new adverse effects were noticed in the study and use of CSE-1034 alone or in combination with Colistin was safe, provided Colistin doses are reduced after initial loading doses. After discharge from ICU, the patients were monitored for cases of reinfection/ relapse and no such relapse or super infection was observed in any of the patients.

Further, no significant changes in PT/INR were observed in any of the patients treated with CSE-1034. This could be well explained by the pharmacokinetic analysis study done on CSE-1034 which has evaluated the plasma concentration of different components of CSE-1034 at various time points after giving CSE-1034 3 g BD dose regimen using LC-MS/MS method [24]. The maximum concentration of EDTA achieved in blood was 23.6 µg/mL which is far less than the concentration (1.8 mg/ml) required to prevent blood clotting [24]. As the concentration is very less, so that could be the reason that there was no visible effect on prothrombin time in CSE-1034 treated patients. Moreover, none of the previous clinical study based on CSE-1034 has reported any abnormal bleeding event in any of the patients treated with this drug [7].

5. CONCLUSION

Usually BL-BLI combinations are used as first line therapy in healthcare associated infections. This trend is now changing very fast because of the increasing resistance to BL-BLI and the switchover to penems (the last resort) is frequent. In this scenario, this study adds a lot of value to the medical community by suggesting that AAE, CSE-1034 which is supplemented with antibiotic resistance breaker EDTA and favorable safety profile can be considered as an effective replacement.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Khajuria A, Praharaj AK, Kumar M, Grover N. Carbapenem resistance among enterobacter species in a Tertiary Care Hospital in Central India. Chemother Res Pract; 2014.
   DOI: 10.1155/2014/972646
2. Cornaglia G, Rossolini GM. The emerging threat of acquired carbapenemases in Gram-negative bacteria. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2010;16:99–101.
   DOI: 10.1111/j.1469-0691.2009.03114.x
3. Harris PNA, Tambyah PA, Paterson DL. β-lactam and β-lactamase inhibitor combinations in the treatment of extended-spectrum β-lactamase producing Enterobacteriaceae: Time for a reappraisal in the era of few antibiotic options? Lancet Infect Dis. 2015;15:475–85.
   DOI: 10.1016/S1473-3099(14)70950-8
4. Venkataraman R, Divatia JV, Ramakrishnan N, Chawla R, Amin P, Gopal P, et al. Multicenter observational study to evaluate epidemiology and resistance patterns of common intensive care unit-infections. Indian J Crit Care Med. 2018;22:20.
   DOI: 10.4103/ijccm.IJCCM_394_17
5. Díaz-Martín A, Martínez-González ML, Ferrer R, Ortiz-Leyba C, Piacentini E, Lopez-Pueyo MJ, et al. Antibiotic prescription patterns in the empiric therapy of severe sepsis: Combination of antimicrobials with different mechanisms of action reduces mortality. Crit Care Lond Engl. 2012;16:R223.
   DOI: 10.1186/cc11869
6. Kumar A, Safdar N, Kethireddy S, Chateau D. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: A

meta-analytic/meta-regression study. Crit Care Med. 2010;38:1651–64.
DOI: 10.1097/CCM.0b013e3181e96b91

7. Chaudhary M, Mir MA, Ayub SG. Safety and efficacy of a novel drug elores (ceftriaxone + sulbactam + disodium edetate) in the management of multi-drug resistant bacterial infections in tertiary care centers: A post-marketing surveillance study. Braz J Infect Dis. 2017;21:408–17.
DOI: 10.1016/j.bjid.2017.02.007
8. Chaudhary M, Ayub SG, Mir MA. Comparative efficacy and safety analysis of CSE-1034: An open labeled phase III study in community acquired pneumonia. J Infect Public Health; 2018.
DOI: 10.1016/j.jiph.2018.04.006
9. Cleveland Clinic Hospital–Acquired, Health Care–Associated, and Ventilator–Associated Pneumonia. Virtual Med Sch n.d.
Available:https://teachmemedicine.org/cleveland-clinic-2/
(Accessed May 8, 2018)
10. Sattler FR, Weitekamp MR, Ballard JO. Potential for bleeding with the new beta-lactam antibiotics. Ann Intern Med. 1986; 105:924–31.
11. Sattler FR, Weitekamp MR, Sayegh A, Ballard JO. Impaired hemostasis caused by beta-lactam antibiotics. Am J Surg. 1988;155:30–9.
12. Finnegan S, Percival SL. EDTA: An Antimicrobial and Antibiofilm Agent for Use in Wound Care. Adv Wound Care. 2015;4: 415–21.
DOI: 10.1089/wound.2014.0577.
13. Sharma M, Visai L, Bragheri F, Cristiani I, Gupta PK, Speziale P. Toluidine blue-mediated photodynamic effects on staphylococcal biofilms. Antimicrob Agents Chemother 2008;52:299–305.
DOI: 10.1128/AAC.00988-07
14. Yoshizumi A, Ishii Y, Livermore DM, Woodford N, Kimura S, Saga T, et al. Efficacies of calcium-EDTA in combination with imipenem in a murine model of sepsis caused by Escherichia coli with NDM-1 β-lactamase. J Infect Chemother Off J Jpn Soc Chemother. 2013;19:992–5.
DOI: 10.1007/s10156-012-0528-y
15. Chaudhary M, M S, Kumar S, V K. Catering ESBL resistance challenge through strategic combination of ceftriaxone, sulbactam and ethylenediaminetetraacetic acid. Int J Drug Dev Res. 2015;4.
16. Chaudhary M, Kumar S, Payasi A. A novel approach to combat acquired multiple resistance in *Escherichia coli* by using EDTA as efflux pump inhibitor. J Microb Biochem Technol. 2012;4.
DOI: 10.4172/1948-5948.1000082
17. Chaudhary M, Payasi A. Comparative efficacy of antibiotics in biofilms eradication formed by ESBL and non ESBL producing micro-organisms. Int J Drug Dev Res. 2012;4.
18. Chaudhary M, Payasi A. Role of EDTA and CSE1034 in curli formation and biofilm eradication of *Klebsiella pneumoniae*: A comparison with other drugs. J Antibiot (Tokyo) 2012;65:631–3.
DOI: 10.1038/ja.2012.82
19. Kumar M, Chaudhary S, Makkar DK, Garg N, Chugh S. Comparative antimicrobial efficacy evaluation of a new product elores against meropenem on gram negative isolates. Asian J Pharm Clin Res. 2015; 8:251–4.
20. Chaudhary M, Payasi A. Molecular characterization and *in vitro* susceptibilities of β-lactamase producing *Escherichia coli*, *Klebsiella* species, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* to CSE1034 and other β-lactams. Asian Pac J Trop Med. 2014;7S1:S217-223.
DOI: 10.1016/S1995-7645(14)60235-2
21. Bhatia P. Alternative empiric therapy to carbapenems in management of drug resistant gram negative pathogens: A new way to spare carbapenems. Res J Infect Dis. 2015;3:2.
DOI: 10.7243/2052-5958-3-2
22. Verma S. A retrospective study to evaluate the efficacy of a new antibiotic adjuvant entity (β-lactam/β-lactamase inhibitor/ adjuvant disodium edetate combination) for management of sepsis. Res J Infect Dis. 2015;3:3.
DOI: 10.7243/2052-5958-3-3
23. Patel I, Hussain R, Khan A, Ahmad A, Khan MU, Hassalai MAA. Antimicrobial

resistance in India. J Pharm Policy Pract. 2017;10.
DOI: 10.1186/s40545-017-0118-6

24. Pharmacokinetics and pharmacodynamics of elores in complicated urinary tract infections caused by extended spectrum beta-lactamase strains. International Journal of Pharmaceutical Sciences and Research n.d.
Available:http://ijpsr.com/bft-article/pharmacokinetics-and-pharmacodynamics-of-elores-in-complicated-urinary-tract-infections-caused-by-extended-spectrum-beta-lactamase-strains/
(Accessed May 8, 2018)

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/25711