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ORIGINAL RESEARCH

Cefepime-induced neurotoxicity in non-critically ill medical patients: a retrospective cohort study

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Abstract

Studies had reported the association between cefepime and neurotoxicity. The neurotoxicity incidence was well documented regarding the intensive care unit (ICU). This study was aimed to evaluate the incidence and characteristics of neurotoxicity caused by cefepime in the medical patients. A retrospective study was conducted on the medical patients treated with cefepime. Patients having received cefepime were eligible for the screening. Exclusion criteria were as follows: admitted in ICU, Alzheimer's disease, admitted with the altered mental status because of any cause or epilepsy history. Naranjo adverse event scale described the probability of adverse events in suspected cases and categorized as definite, probable, possible and doubtful. A total of 601 patients were screened wherein 93 met the inclusion criteria. The mean age (±standard deviation (SD)) was 56 years (±17). The patients' majority was male (66%) with the normal kidney function (73%). Common comorbidities included hypertension (60%) and diabetes (40%). Only 2 patients (2%) had developed neurological symptoms. The cases were carefully evaluated where one was doubtful and the other possibly had cefepime-induced neurotoxicity. The neurotoxicity incidence among medical patients was low, and might relate to the disease states affecting central nervous system. Hence, a careful evaluation of other possible causes for neurological symptoms deemed necessary while being on cefepime therapy.

Keywords

Cefepime; Neurotoxicity; Seizure; Altered mental status; Adverse event

1. Introduction

Cefepime is a broad spectrum fourth generation cephalosporine employed in treating gram negative and gram-positive bacterial infections, which include but not limited to pneumonia, neutropenic fever, complicated urinary tract infections and uncomplicated skin and soft tissue infections [1]. Studies have reported the association between cefepime exposure and neurotoxicity [2–6], attributed to its ability for penetrating the blood brain barrier (BBB) [7, 8]. Cefepime is mostly eliminated *via* the renal excretion with an average half-life of two hours. The excretion time increases up to 13 hours with renal impairment [9]. The patients with impaired renal functions thus receive an adjusted cefepime dose. The failure in renal adjustment of cefepime dose may accumulate cefepime and develop neurotoxicity, although not observed in all studies [10]. Other theories suggest that cefepime can block or decrease ϒ-aminobutyric acid (GABA) release to induce neurotoxicity [5]. Cefepime usage is prevalent in ICU patients where neurological manifestations are common and associated with drug toxicity [11–14]. Other neurotoxicity confounders include infections, electrolyte imbalance, hypoglycemia and alcohol withdrawal. The incidence of cefepime induced neurotoxicity is established in ICU patients with its rate between 3 to 15% [15]. Its incidence is unknown in medical patients. This study determines the incidence and characteristics of cefepime-induced neurotoxicity in medical patients.

2. Materials and methods

2.1 Study settings, design, and data source

A retrospective study was conducted *via* the chart review at Banner-University Medical Center-South (tertiary academic center of 250 bed capacity) in Tucson, Arizona, USA. Patients receiving cefepime for presumed or confirmed bacterial infections from October 2017 to December 2018 were screened for eligibility. The eligibility criteria included the patients who received cefepime for presumed or confirmed bacterial infections for more than 72 hours. The exclusion criteria were as follows: patients in ICU, Alzheimer's disease, admitted with altered mental status because of any cause (*e.g.*, alcohol intoxication), or epilepsy history. Information technology team generated the patients list. A random selection methodology was employed for screening and eligibility to minimize the selection bias and enable the generalization of findings [16].

2.2 Data collection and variables

Data were manually collected from the electronic health system (Cerner®). A structured data collection tool was employed to collect the data using excel. Patients were screened according to the eligibility criteria. The demographic data like age and sex were collected for the eligible patients. Furthermore, the clinically relevant data such as comorbidities, admission diagnosis, creatinine clearance, chronic kidney disease, cefepime indication, concomitant antibiotics and medications, cefepime dose (grams/day), cefepime administration method (in case of infusion), cefepime therapy duration and isolated microorganisms from the primary source of infection were collected.

2.3 Sample size calculation

At least 73 patients were included assuming an incidence of 5% for cefepime induced neurotoxicity (with 95% confidence interval of 0 to 10%). This assumption was lower than that of reported in ICU setting (the highest reported as 15%) [17].

2.4 Definitions

Cefepime-induced neurotoxicity was defined based on the following one or more symptoms experienced by a patient after cefepime initiation: seizure, altered mental status, myoclonus, agitation and delirium [18]. Creatinine clearance calculation was made by the Cockroft-Gault equation [19]. Chronic kidney disease was defined as per the most recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines [20]. The Adverse Drug Reaction (ADR) Probability (Naranjo) Scale was employed for the causality assessment where score of $\geq$9 was considered definite, 5 to 8 probable, 1 to 4 possible and 0 doubtful [21].

2.5 Statistical analysis

Descriptive analyses were used means with standard deviations ($\pm$SD) to report the continuous variables. Percentages and frequencies were employed for the categorical variables. All analyses were conducted by the Statistical Package for Social Sciences (SPSS) statistics® version 25 (IBM Corp, Armonk, NY, USA).

3. Results

A total of 3754 cefepime orders were identified, from where 601 patients were screened through random selection method and only 93 met the inclusion criteria (Fig. 1). The mean ($\pm$SD) age was 56 years ($\pm$17) and majority was male (66%). Hypertension (60%) and diabetes (40%) were the most encountered comorbidities. Vancomycin was the concomitant antibiotic employed with cefepime in 91% cases. The common isolated microorganisms from this patient population were *Escherichia coli* (E. coli) (10%), *Methicillin resistant staphylococcus aureus* (MRSA) (8%), *Klebsiella pneumoniae* (KP) (6%) and *Methicillin sensitive staphylococcus aureus* (MSSA) (5%). The baseline characteristics given in Table 1. The osteomyelitis (18%) and pneumonia (16%) were the common indications treated by cefepime in general medical ward (Table 2). Cefepime mean ($\pm$SD) therapy duration was 4.8 days ($\pm$2.9) with mean ($\pm$SD) dose of 4 grams/day ($\pm$1.4) (Table 2). Only two (2%) of 93 patients were presented with doubtful and possible cefepime-induced neurotoxicity. The following offered a detailed discussion of the treatment course of two identified patients.

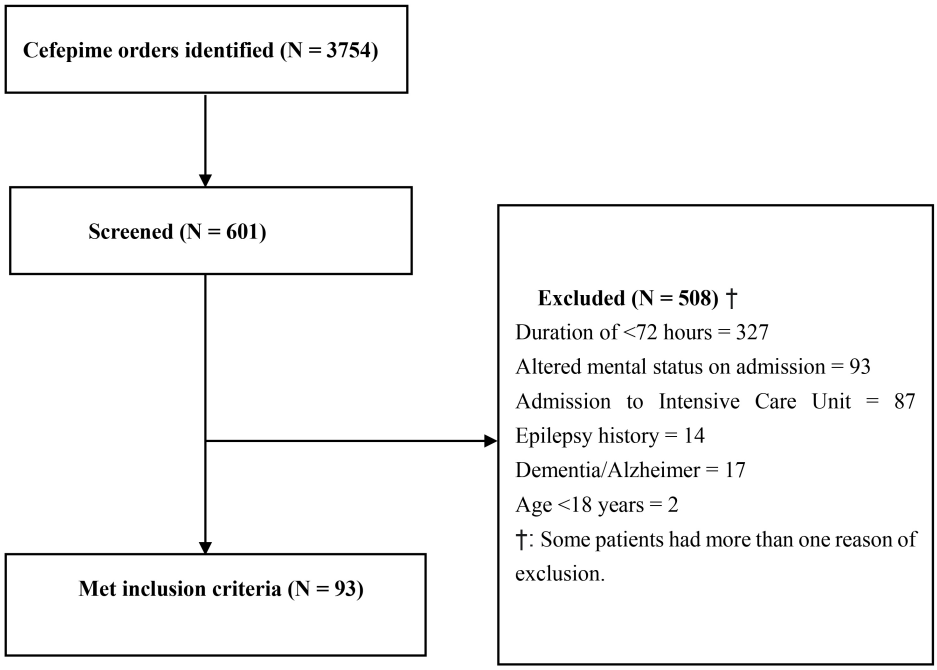

FIGURE 1. Flowchart of patient identification and screening. A list of patients received cefepime was generated (N = 3754) and eligible patients (N = 601) were screened through random selection methodology. Only (N = 93) met the inclusion criteria.

TABLE 1. Demographic and clinical characteristics (n = 93).

Study variable	Value
Age (yr), mean (±SD)	56 (17)
Female, n (%)	32 (34)
Comorbidities, n (%)	Freq (%)
Hypertension	56 (60)
Diabetes	37 (40)
Hyperlipidemia	24 (26)
Gastroesophageal intestinal diseases	14 (15)
Respiratory diseases	16 (17)
Psychiatric diseases	16 (17)
Cardiac diseases	12 (13)
Central nervous system diseases	6 (6)
Arrhythmia	5 (5)
CrCl (mL/min), mean (±SD)	92 (43.4)
Chronic kidney disease stage, n (%)	Freq (%)
Normal kidney function (G1)	68 (73)
G2	2 (2)
G3a	15 (16)
G3b	4 (4)
G4	4 (4)
Concomitant antibiotics, n (%)	Freq (%)
None	8 (8)
Vancomycin	85 (91)
Metronidazole	29 (31)
Clindamycin	11 (11)
Azithromycin	8 (8)
Doxycycline	3 (3)
Oseltamivir	2 (2)
Others	7 (7)
Isolated microorganisms[†], n (%)	Freq (%)
E. coli	10 (21)
MRSA	8 (17)
Klebsiella pneumoniae	5 (10)
MSSA	5 (10)
Multiple microorganisms	5 (10)
Others	17 (36)

[†]*Eight patients had no cultures and 46 had negative cultures. Percentage calculation was based on 47 isolates. Ten patients had two or more isolated microorganisms.*
SD: Standard deviation; E. coli: Escherichia coli; MRSA: Methicillin resistant staphylococcus aureus; MSSA: Methicillin sensitive staphylococcus aureus.

TABLE 2. Cefepime characteristics (N = 93).

Study variable	Value
Cefepime dose (g/day), mean (±SD)	4.0 (1.5)
Cefepime therapy duration (days), mean (±SD)	4.8 (2.9)
Cefepime indication, n (%)	Freq (%)
Osteomyelitis	18 (19)
Pneumonia	16 (17)
Bacteremia	10 (10)
Cellulitis	9 (9)
UTI	9 (9)
Septic joints	6 (6)
Intra-abdominal infection	7 (7)
Sepsis	5 (5)
Others	28 (30)
Cefepime continuous infusion	3 (3)
Cefepime neurotoxicity	2 (2)

SD: Standard deviation; UTI: Urinary tract infection.

3.1 Case 1 (Table 3)

The first patient was a 58-year man with medical history of hypertension (HTN), type II diabetes mellitus, hyperlipidemia and cerebrovascular accident (CVA). He was transferred from another facility and admitted because of the possible urosepsis. The patient failed outpatient oral antibiotic therapy and the urine culture grew staphylococcus aureus. Additionally, the cellulitis on left-hand finger was identified as another cause of sepsis. Blood cultures were collected for the identification and susceptibility. The empiric antibiotic regimen consisted of vancomycin and cefepime (4 grams/day) to cover MRSA, and pseudomonas aeruginosa for the urinary tract infection. The blood cultures became positive for MSSA after three days of admission. Magnetic resonance imaging (MRI) was requested because of the reported back pain. The results exhibited spinal epidural abscesses (C2–T2), and osteomyelitis (L5–S1). Cefepime and vancomycin were discontinued on the fourth day of admission, and nafcillin was started for MSSA. The patient after four days of cefepime discontinuation developed acute mental status changes, bowel incontinence, urinary retention and decreased rectal tone for raising the concern of cord compression. The patient after nine days of admission underwent epidural abscesses drainage, and C3–C4 laminectomies. He remained on nafcillin which changed to cefazolin (2 grams every 8 hours) on fifth day of surgery for the duration of 8 weeks. The postoperative course was simple, and the patient was discharged on cefazolin to finish the course for bacteremia, osteomyelitis, and drained epidural abscesses. The Naranjo Adverse Drug Reaction (ADR) Probability Scale was 0 to indicate doubtful ADR, given the presence of other neurotoxicity causes (epidural abscesses, septicemia and spinal cord compression in this patient), and the disproportionate incidence of neurotoxicity.

TABLE 3. Case reports of two patients with cefepime-induced neurotoxicity.

Patient	Gender /Age	Neurotoxicity	Other Antibiotics	Cefepime EI	Cefepime dose	Cefepime duration	Other comorbidities	CrCl	Confounders	Naranjo ADR scale	Microorganism
1	M/58	Acute Encephalopathy (4 days after cefepime discontinuation)	Vancomycin	No	4 grams/day	4 days	DM, HTN, HLD, CVA	>90 mL/min	Spinal epidural abscesses, multiple septic emboli + S/P Laminectomies surgery	Doubtful	MSSA
2	F/71	Myoclonic jerking movement, Sweating of both arms	Azithromyc	No	4 grams/day	4 days	CHF, Atrial fibrillation, HTN, CVA, DM, OSA and prior DVTs	52 mL/min	Hypoglycemia	Possible	Negative culture

M: Male; F: Female; EI: Extended infusion; CrCl: Creatinine clearance; DM: Diabetes Mellitus; HTN: Hypertension; HLD: Hyperlipidemia; CVA: Cerebral vascular accident; CHF: Congestive heart failure; OSA: Obstructive sleep apnea; DVT: Deep venous thrombosis; S/P: Status post; MSSA: Methicillin sensitive staphylococcus aureus; ADR: Adverse Drug Reaction.

3.2 Case 2 (Table 3)

The second patient was a 71-year woman with medical history of atrial fibrillation, congestive heart failure (CHF), HTN, type II diabetes mellitus (DM) and deep venous thrombosis (DVT). She was presented to the hospital with acute onset of breath shortness. Patient's family reported that she was complaining of non-productive cough and subjective fever. Additionally, lower extremity swelling was noted with the right greater than the left, and the right lower extremity erythema, and pain. Physical examination of the patient revealed to have diffuse crackles throughout her lung fields, lower extremity edema and tenderness attributed to venous stasis because of the DVTs history. Patient also had a chronic right heel ulcer with no apparent infection. After the patient was admitted and diagnosed with multifocal pneumonia, she was started with azithromycin (500 mg/day) and cefepime (4 grams/day). The patient was not appropriately responding to the commands on day three of admission, and had myoclonic jerking movements with sweating of both arms. Further investigations depicted the patient having hypoglycemia (fingerstick blood glucose of 60 mg/dL). Dextrose (10%) bolus followed by infusion was immediately started to correct the blood glucose (repeated fingerstick blood glucose of 213 mg/dL) and improve the symptoms. Stroke was ruled out because of the negative MRI for acute intracranial abnormality. Neurological consultations were made to investigate and seek further guidance pertaining to the myoclonic jerking movements. The neurology team recommended to de-escalate the current antibiotic regimen and switch to lesser neurotoxic antibiotic regimen. Cefepime was discontinued on the fourth day of admission and changed to amoxicillin-clavulanic acid (875 mg twice a day) and azithromycin (500 mg/day). The neurology team recommended electroencephalogram (EEG) monitoring on the fifth day of admission to detect seizure activity only if the patient mentation and myoclonic jerking did not improve. Patient continued to clinically improve and thus discharged for home. The Naranjo ADR scale was 2 to indicate a possible ADR.

4. Discussion

The findings of this study did not show clear association between cefepime and neurotoxicity in the non-critically ill patients. The incidence of neurotoxicity after excluding confounders was not as high as in the previous studies [3, 5, 22]. Only two patients experienced neurotoxicity (one doubtful and one possible) (Table 3). Both patients had multiple clinical conditions to likely cause neurotoxicity. For instance, the first patient had spinal epidural abscesses that could result in direct cord compression and develop neurological deficit. The second patient had hypoglycemia with improvements in signs and symptoms upon dextrose administration. The temporality was difficult to establish because of the coinciding clinical conditions. The cefepime neurotoxicity was highly prevalent in impaired renal function patients, while 73% of patients had normal kidney function. Another factor increasing the likelihood of cefepime neurotoxicity was the advanced age. Our patient population was in mid 50s. Thus, more patients with cefepime induced neurotoxicity could have been detected if there were older patients with impaired renal function.

Wong *et al.* [23] reported the first case of cefepime-induced neurotoxicity following its approval in 1999. The patient was on hemodialysis and the cefepime dose was not appropriately adjusted [23]. Several studies were reported following this case report for emphasizing the importance of dose adjustment in renal impairment patients [24–26]. The United States Food and Drug Administration (FDA) in June 2012 issued a safety communication letter for health care providers to adjust the cefepime dose in renally impaired patients [27]. Grahl *et al.* [28] conducted a retrospective study to determine the association between antibiotics classes and the development of ICU delirium. Cefepime was not associated with delirium after controlling the commonly encountered confounders in ICU [28].

The heterogeneity and coexistence of other diseases implicated because of the neurotoxicity of reported cases and studies had hindered in providing the true estimates for incidence of cefepime-induced neurotoxicity. For instance, Fugate *et al.* [22] conducted a retrospective study to characterize the cefepime-induced neurotoxicity in critically ill patients. They used a modified Delphi method for categorizing the patients with cefepime-induced neurotoxicity into three groups: definite, probable and possible. Authors discussed other neurotoxicity causes which could be implicated to create challenges in establishing association due to the complexity and nature of intensive care unit (ICU) patients. The authors did not explore the impact of such confounding diseases by excluding or controlling them *via* a univariate regression model [22]. Tanaka *et al.* [3] determined the prevalence of convulsions following the cefepime exposure, and compared it to meropenem. Similar to the study by Fugate *et al.* [22], all the patients having developed neurotoxicity had established diseases involving the CNS. Singh *et al.* [29] conducted a case-control study to determine the factors associated with acute encephalopathy in ICU settings. Cefepime usage was independently associated with acute encephalopathy [29]. Patients with acute kidney injury and chronic kidney disease were at higher risk [29]. Several studies correlating neurotoxicity with cefepime were mainly in the patients with certain degree of impaired kidney function [30–37], however neurotoxicity was also reported in patients of normal kidney function [38, 39].

To the best of knowledge, it was the first study conducted on medical patients where confounding variable was adjusted and the other such studies made in ICU populations had overlooked it. There were still many limitations. First, the duration of cefepime administration in this study was around 5 days compared to the other studies having relatively longer times to detect the adverse effects [15, 22, 40]. Second, the therapeutic drug monitoring (TDM) might appeal given the observed association between higher levels and neurotoxicity [41–46], however, it was not available at our institution. The neurotoxicity event in our sample was low. A regression analysis was not possible to explore the associations of neurotoxicity development and the variables of interest. Nonetheless, this cohort of patients consisted of medical patients to possibly restrict the enrollments, however, at the expense of sample size [47].

5. Conclusions

The incidence of cefepime-induced neurotoxicity was low in the medical patients. The probability of neurotoxicity as an adverse event for suspected cases was also low. A careful assessment and evaluation of other causes of neurotoxicity were recommended while on the cefepime therapy.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed for this study are included in this published article are available upon request.

AUTHOR CONTRIBUTIONS

ASA—study conception and design, data collection, interpretation of results, and manuscript preparation.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the University of Arizona Institutional Review Board (approval # 1905614519). Consent to participate was waived as the study involved no more than minimal risk.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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