

Case Report

Looking beyond the Obvious: Cefepime-induced Nonconvulsive Status Epilepticus

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Abstract

Cephalosporins are a commonly used class of antibiotics in various types of infections. Cefepime, a fourth-generation cephalosporin, has been reported to cause neurotoxicity, which can present itself as varied manifestations. Nonconvulsive status epilepticus (NCSE) is a rare manifestation of this neurotoxicity. This condition often proves difficult to diagnose because it is chiefly an electroencephalogram-based diagnosis. The authors report a case of cefepime-induced NCSE in a 57-year-old female patient with compromised renal status.

Keywords: Cephalosporins, encephalopathy, neurotoxicity, seizures

INTRODUCTION

Cefepime, a fourth-generation cephalosporin, is being prescribed quite commonly of late, especially in individuals with immunosuppression. Cefepime, a cephalosporin, belongs to beta lactam antibiotics along with penicillins, aztreonam, and carbapenems. While it has quite a favorable toxicity profile, there have been a few reports lately of its neurotoxic potential. Its ability to cause neurotoxicity increases in a setting of renal failure or a preexisting neurological disorder.^[1]

Nonconvulsive status epilepticus (NCSE) is a condition characterized by continuous seizures in the absence of convulsions for a duration beyond 30 min without complete interictal recovery. The clinical picture is highly variable making detection and management of this condition tricky. Availability of electroencephalogram (EEG) is vital for detection of this condition. Management of NCSE is mainly based on intensive care, antiepileptic agents, and treatment of the cause, in addition to withdrawal of the offending agent.^[2] Discussed below is a case of NCSE caused by cefepime.

CASE REPORT

A 57-year-old female, with existing comorbidities of type 2 diabetes mellitus and hypertension, came to the outpatient department of our tertiary care center, with chief complaints of fever and burning micturition for the past week. On

reviewing her case files, it was learnt that she had consulted at our hospital approximately a month ago with similar complaints, when she was admitted and diagnosed to have emphysematous pyelonephritis, and was administered oral faropenem, following which she became asymptomatic, and was discharged.

During the current admission, the patient was started on intravenous cefepime 2 g thrice daily, along with subcutaneous insulin, oral enalapril, and oral ondansetron. Her urine culture grew *Escherichia coli*, which was sensitive to cefepime. On day 10 of this course of treatment, the patient exhibited altered sensorium. Pupils were bilaterally reactive; Doll's eye reflex was found to be positive, and her Glasgow Coma Scale evaluation revealed a score of E₂V₁M₄. The patient was intubated and shifted to the intensive care unit. Computed tomography scan of the brain showed small vessel ischemic changes, while lumbar puncture findings were within normal limits. EEG [Figure 1] showed continuous generalized

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epileptiform abnormalities, suggestive of NCSE. She was started on intravenous levetiracetam 1 g loading dose and 750 mg (twice daily) maintenance dose. In the view of the patient's persistent drowsy state, fosphenytoin was added.

As any alternate etiology causing NCSE was not identified, we suspected cefepime-induced NCSE. The patient was taken off of cefepime and, instead, intravenous meropenem was initiated, according to the results of her urine culture and sensitivity. The patient's sensorium improved and was extubated after 4 days. Repeat EEG was normal [Figure 2]

and levetiracetam was changed to oral route; fosphenytoin was tapered and stopped.

The causality of the adverse drug reaction was analyzed using Naranjo algorithm, which gave us a score of 7, denoting "probable" causality.

DISCUSSION

Cefepime is a fourth-generation cephalosporin that is commonly in use for its broad spectrum coverage of several

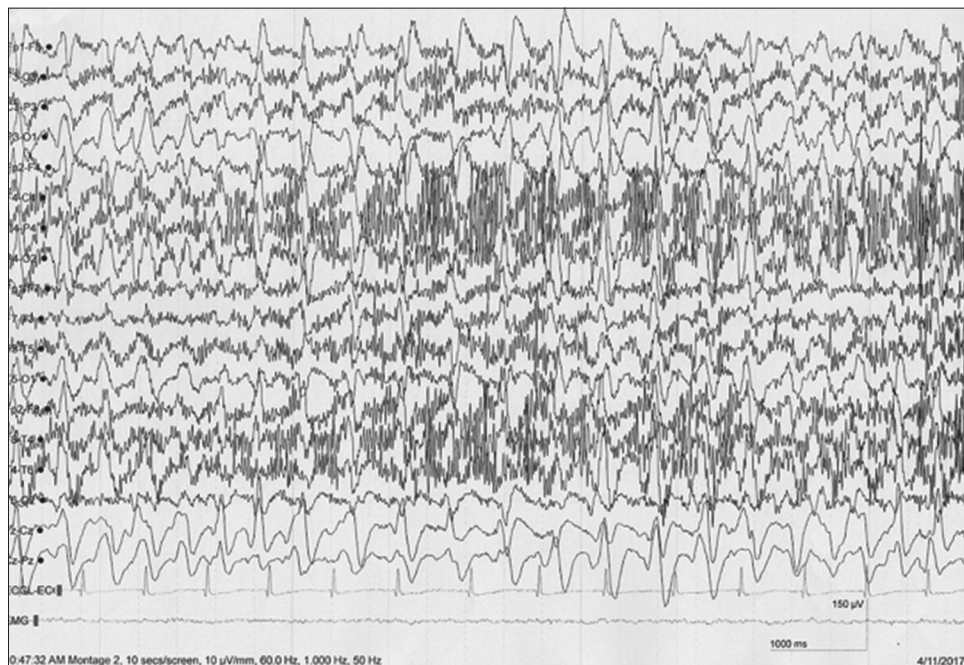


Figure 1: Preliminary electroencephalogram of the patient (during cefepime administration), suggestive of nonconvulsive status epilepticus



Figure 2: Repeat electroencephalogram of the patient (after discontinuing cefepime), depicting normalization

infections. It is excreted majorly by the renal clearance pathway, thus posing risks of toxicity in patients with inadequate renal function.^[1] There have been a few instances of similar episodes reported in the past. In 2012, US-Food and Drug Administration released a safety statement, which revealed that 59 cases of NCSE were reported following the usage of cefepime from 1996 (year of approval of cefepime) to February 2012. Of these 59 patients, 58 had some degree of renal impairment.^[3,4] In our present scenario, the patient had abnormally elevated renal function parameters.

NCSE and other neurotoxic features have been reported to occur anywhere between 1 and 24 days following cefepime administration, with a mean of around 7 days. Furthermore, it has been analyzed that a mean period of 3 days passes by between the onset of neurological symptoms and actual diagnosis.^[3,5] In our case, the time period between initiation of cefepime and diagnosis of neurological symptoms was 10 days, which falls in the above-mentioned bracket.

Most patients of cefepime-induced NCSE have brief episodes of convulsive seizures (in the form of myoclonus) preceding the actual NCSE.^[1] This was observed in our patient as well. The most widely accepted modality to diagnose cases of NCSE is the use of EEG, which was also done in our patient's case.^[6,7]

Although the authors have not made a mechanistic analysis, we would like to put forward the hypothesis proposed by various other articles in the past. Cefepime could act as a GABAA antagonist, which results in a decrease in the GABAergic transmission. This leads to disinhibition that results in overexcitation of neurons, ultimately resulting in seizures and other neurotoxic features.^[3,8]

CONCLUSION

It is essential to make necessary adjustments in dosage when initiating cephalosporins, especially cefepime, in elderly patients or in patients with compromised renal status. Furthermore, a vigilant eye should be focused on the mental

status of the patients, and emergency EEG should be performed in patients with altered mental status. Further, there may be a role for measuring serum concentrations of cefepime in such patients. To conclude, it is essential to remember that neurological toxic features are not always those that are visible and obvious. Sometimes, it is necessary to look beyond the obvious.

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Conflicts of interest

There are no conflicts of interest.

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