Cefepime-induced non-convulsive status epilepticus

Walter R. Duarte-Celada MD, Smathorn Thakolwiboon MD, Jie Pan MD, Tulio Bueso MD, Jannatul Ferdous MD

Abstract

Cefepime-induced non-convulsive status epilepticus (NCSE) can develop in patients with advanced age, renal impairment, and previous central nervous system disorders. Its clinical presentation varies from confusion, mutism, and decreased level of consciousness to coma. The typical electroencephalogram (EEG) findings are generalized spike and wave discharges of 1–3 Hz. We present a case series of 4 patients with cefepime-induced NCSE, including the clinical presentation and EEG findings. Electroencephalograms should be part of the workup of acute confusional state in patients on this antibiotic, and physicians should be aware of this uncommon complication.

Keywords: Non-convulsive status epilepticus, cefepime, confusion, mutism, electroencephalogram.

Introduction

Non-convulsive status epilepticus (NCSE) has been described as an adverse event during treatment with cefepime, a fourth-generation cephalosporin. Cefepime-induced NCSE affects mainly patients with advanced age, impaired renal function, and pre-existing central nervous system (CNS) disorders. Non-convulsive status epilepticus has been more frequently described in recent years given the wide availability of the electroencephalogram (EEG) in most hospitals and the wide use of cefepime, especially in septic patients. Early recognition and prompt treatment of this condition are necessary for better outcomes.

Cases

Case 1: A 72-year-old woman with history of well-controlled epilepsy and chronic kidney disease (CKD) stage III was admitted for community-acquired pneumonia. On admission, cefepime was started as part of her management, but no renal adjustments were done during the hospitalization. On day 2, the patient awoke confused and nonverbal (mute). No significant blood abnormalities were noted, except for decreasing renal function (glomerular filtration rate [GFR] from 37 to 25 mL/min). Computed tomography was unrevealing. Electroencephalogram showed a continuous generalized 2.5-to-3-Hz high voltage spike and sharp wave discharges (Figure 1A). Intravenous lorazepam 2 mg was given. Two minutes later, the patient became verbally responsive, and an EEG showed a substantial improvement (Figure 1B). The GFR on the day of the EEG was 19 mL/min; the cefepime dose was 1 g every 12 hours. Levetiracetam was initiated, and cefepime was discontinued. The patient's mental status fluctuated over the next couple of days until it returned to her baseline.

Case 2: A 54-year-old man with history of hypertension and coronary artery disease was admitted for left foot osteomyelitis, diarrhea, and acute kidney injury. He was started on cefepime on admission, but no renal adjustments were done during the hospitalization. On day 15, he was nonverbal (mute), not following commands, and with his eyes open. No metabolic derangements were noted at that point, except for worsening of his kidney function (GFR from 50 to

Corresponding author: **Walter Duarte**
Contact Information: Walter.Duarte@ttuhsc.edu
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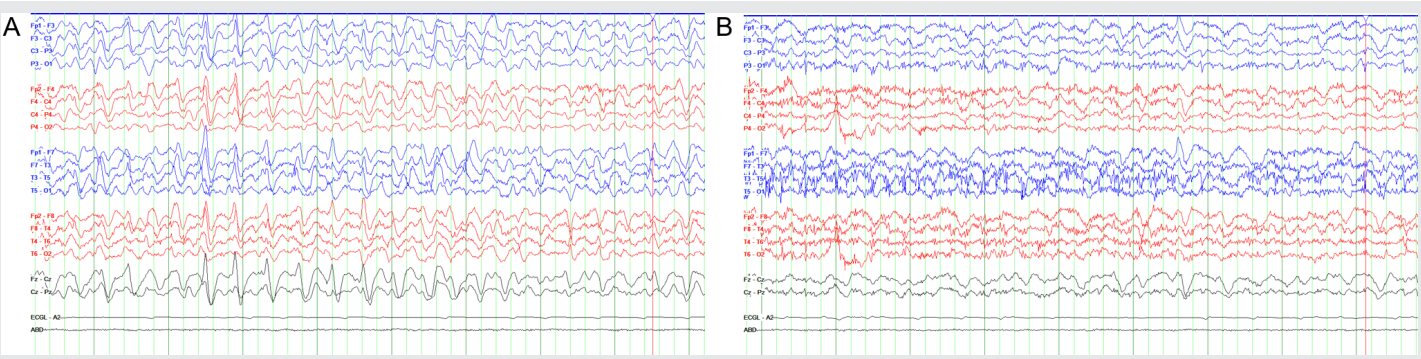

Figure 1. EEG in case # 1 shows: A) Multiple runs of generalized periodic discharges above 2 cycles/second (Hz). The patient's clinical presentation was described as mute, not following commands. B) EEG right after the benzodiazepine challenge, showing abortion of the electrographic seizures. Clinical response was also noted after the benzodiazepine use. This finding confirmed the diagnosis of non-convulsive status epilepticus.

18 mL/min). Computed tomography was unrevealing. Electroencephalogram showed continues generalized 1-to-2-Hz high voltage sharp and slow wave discharges. Benzodiazepine challenge did not produce any clinical or EEG changes. The GFR on the day of the EEG was 40 mL/min. Cefepime was discontinued, and the patient was started on levetiracetam and subsequently on fosphenytoin. Two days after the discontinuation of cefepime, his symptoms improved, and on the third day the patient's mental status went back to baseline.

Case 3: An 82-year-old woman with history of hypertension, diabetes, congestive heart failure (CHF), congenital single kidney, CKD III, and chronic obstructive pulmonary disease was admitted due to CHF exacerbation and respiratory failure. She was started on antibiotics, including cefepime, which was not adjusted for her kidney function. On day 5, the patient developed decreased responsiveness. Laboratory tests were normal except for decreasing renal function; her GRF decreased from 26 mL/min to 20 mL/min. Computed tomography of the head was unrevealing. An EEG showed continuous generalized 3-or more-Hz periodic spike and wave discharges. The benzodiazepine challenge did not change her EEG or clinical status. The GFR on the day of the EEG was 29 mL/min; the cefepime dose was 2 g every 8 hours. Cefepime was discontinued, and she was started on levetiracetam and subsequently valproic acid, phenytoin, and lacosamide. No intubation or sedation was attempted due to her DNR status. The patient died from a cardiac arrest on day 10 of hospitalization.

Case 4: A 62-year-old woman with a history of end-stage renal disease on hemodialysis, diabetes, hypertension, and liver cirrhosis was admitted for disorientation. She was diagnosed with urosepsis and was started on cefepime. She was arousable and able to follow commands on arrival. The cefepime dose was not adjusted based on her renal function. On day 3 of hospitalization, she was lethargic and did not follow commands. Her renal function had slightly improved from admission (GFR 21 mL/min to 31 mL/min). Her ammonia level was normal. Computed tomography of her head showed no acute findings. An EEG showed rhythmic sharply contoured waves of 1–2 Hz. A benzodiazepine challenge was negative. Cefepime (2 g every 8 hours) was discontinued. She was started on levetiracetam and phenytoin. Her EEG and clinical status improved 2 days later. The patient's hospitalization was complicated by pneumonia, candidemia, and hypercapnic respiratory failure. She was intubated, was unable to be weaned from the ventilator, and was discharged to a long-term acute care facility.

Discussion

Cefepime is a broad-spectrum antibiotic, eliminated by the kidneys. Competitive antagonism with gamma

amino butyric acid (GABA) is possibly responsible for the neurotoxicity and neuro-excitability, including NCSE.[1] The frequency of NCSE in patients with cefepime neurotoxicity has been reported between 25 to 64%.[1,2] The major risk factors for cefepime neurotoxicity are advanced age, renal dysfunction, excessive cefepime dose, and pre-existing central nervous system disorders.[1] Cefepime is primarily cleared by the kidneys, making patients with renal insufficiency prone to neurotoxicity due to longer half-lives.[2] All our cases had impaired renal function, and none received a renal-adjusted dose of cefepime. Only one patient had a remote history of seizures. The interval of onset from cefepime exposure to NCSE development was from 2 to 15 days, similar to other series.[2,3]

Cefepime-induced NCSE may present as confusion, agitation, hallucinations, decreased level of consciousness, mutism, and aphasia; the last 2 presentations are rarely reported in literature.[3,4] Electroencephalographic findings of NCSE include typical sharp waves, atypical sharp waves, multiple sharp waves, and rhythmic delta waves, sometimes making difficult to differentiate NCSE from profound metabolic encephalopathy.[2,5] As described in our cohort, generalized periodic discharges has been the most frequently encountered pattern in other studies.[2]

Treatment includes cefepime discontinuation or dose reduction, antiepileptic administration, and in some cases hemodialysis.[1] Positive outcomes are reported with prompt discontinuation of the offending drug and use of anti-epileptic drug.[3] In patients with late discontinuation of cefepime, there is a tendency toward worse outcomes.[2] A high level of suspicion is necessary for a prompt diagnosis and treatment of this condition, which can contribute to patient's prognosis. A benzodiazepine challenge can help physicians to differentiate this condition from other metabolic disorders that could present with a similar clinical picture of altered mental status and EEG abnormalities.

Conclusions

Non-convulsive status epilepticus is a recognized adverse effect of cefepime. The classic triad for cefepime-induced NCSE includes older patients with impaired renal function and prior CNS morbidity. The clinical presentation of cefepime-induced NCSE varies and can include atypical presentations like aphasia and mutism. An EEG should be part of the workup of acute confusional state in patients with this triad and on this antibiotic.

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From: Department of Neurology (WDC, JF, TB), Texas Tech University Health Sciences Center, Lubbock, TX; Department of Neurology (WDC, JF), Covenant Medical Center, Lubbock, TX; Department of Neurology (ST), Mayo Clinic Health System – Franciscan Healthcare, La Crosse, WI; Department of Neurology (JP), Torrance Memorial Physician Network, Torrance, CA
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