

Cefepime: an Underrecognized Cause of Nonconvulsive Status Epilepticus

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Hospitalized patients with sepsis or severe nosocomial infections are frequently treated empirically with broad-spectrum antibiotics. Cefepime hydrochloride, a fourth-generation cephalosporin, is a common antibiotic of first choice. Its proconvulsant properties are well described in the literature,^{1,2} but its importance as a potential cause of change in mental status is probably underestimated. We report a case of change in mental status related to nonconvulsive status epilepticus (NCSE) caused by the use of cefepime in an elderly, hospitalized patient. Our goal is to raise awareness about this uncommon and still underrecognized complication.

Case Report

A 72-year-old woman with stage III chronic kidney disease secondary to hypertension with a stable creatinine of 1.5 mg/dL (glomerular filtration rate (GFR) estimated by the modification of diet in renal disease (MDRD) at 36 mL/minute/1.73 m²) was admitted to the hospital for worsening of her chronic back pain. She had a past medical history significant for hyperlipidemia, asthma, and peripheral vascular disease, with breast cancer in remission since 1989. She had no history of seizures or cerebrovascular disease. Her medications were ibuprofen, oxycontin, cilastazol, acetaminophen/oxycodone, and an albuterol/ipratropium inhaler. Her physical examination was remarkable only for decreased strength in the right lower extremity. Magnetic resonance imaging (MRI) of the lumbosacral spine showed signs consistent with an inflammatory process at the level of L4-L5. A computed tomography (CT)-guided biopsy was performed and confirmed a diagnosis of osteomyelitis on biopsy. Cultures from the biopsy grew *Pseudomonas aeruginosa* and treatment with intravenous cefepime at a dose of 1 g every 12 hours was initiated. Over the next 3 days, the patient had a gradual worsening of her mental status, leading to pronounced somnolence with occasional episodes of agitation during which she had no focal motor deficits. Her mental status declined to the point of unresponsiveness to simple verbal commands. She had not received any new medications other than cefepime. Her creatinine level was stable throughout this time period at 1.6 mg/dL. No other abnor-

malities were found on laboratory evaluation or on CT and MRI scans of the brain. An electroencephalogram (EEG) was markedly abnormal due to a generalized background slowing and disorganization with frequent bilateral paroxysmal epileptiform discharges, confirming the clinical diagnosis of subclinical generalized status epilepticus. Given that there were no other intrinsic neurological or metabolic reasons for this mental status change, and given that cefepime was the only new medication added before the patient started deteriorating, cefepime was discontinued and treatment for seizures was started with intravenous benzodiazepines. Over the next 2 days, her mental status returned to normal. She was soon discharged to a rehabilitation center.

Discussion

Beta-lactam antibiotics have been described to induce seizures due to their direct and/or indirect inhibition of the gamma-aminobutyric acid (GABA) system.^{1,3} Previous experiments have shown a dose-dependent effect on seizures, and suggest that the cephalosporin with the most pronounced proconvulsant effect is cefazolin.^{1,3}

Cefepime has been associated with neurological side effects such as headache, confusion, hallucinations, agitation, myoclonus, ataxia, seizures, and coma. Another underrecognized but critical side effect is NSCE. This is defined as seizure activity for more than 30 minutes, with cognitive and behavioral changes, but without convulsive clinical manifestations. This complication has been reported in the literature, but it is probably underrecognized.^{3–7} The tendency for cefepime to produce more subclinical activity than the other cephalosporins is not well understood.

Cefepime is mainly eliminated through renal excretion (85%) and displays linear pharmacokinetic properties, thus its dose needs to be adjusted according to renal function. Consequently, in the case of renal dysfunction, accumulation of the drug is proportional to the degree of renal impairment. For NSCE, the most important risk factor is renal impairment, although cases in patients with normal kidney function have been described.^{3–6} Age, pre-existing central nervous system (CNS) disease, sepsis, and

cardiopulmonary bypass have also been reported as possible risk factors for NCSE.¹

Cefepime can accumulate in the cerebrospinal fluid (CSF) in the setting of renal dysfunction, decreased protein-binding capacity (as is sometimes seen in the elderly), and increased blood-brain permeability in the setting of CNS infections. Accumulation of the drug in the CSF can lead to blockade of the GABA-A receptor through a mechanism of competitive antagonism^{1,8}

The onset of NSCE varies between 1 and 16 days after initiation of cefepime therapy.^{3-5,7} It is frequently confused with delirium, since hospitalized patients treated with broad-spectrum antibiotics such as cefepime frequently have other comorbidities and risk factors for delirium.

This can delay the diagnosis of NSCE due to a lack of awareness of this critical complication in the setting of renal dysfunction. In order to quantify the likelihood that the NSCE was related to cefepime and not to other causes, we calculated a Naranjo adverse drug events probability score, which consists of 9 questions on the relationship between the adverse event and the incriminated drug.⁹ Each answer is scored from -1 to +2 points. This score was designed to quantify the strength of the association between any adverse event and a pharmacological agent.

In our patient, the Naranjo score was 7 points, suggesting that the diagnosis of cefepime-induced NCSE was probable.

The diagnosis of NCSE is made through a combination of a high index of clinical suspicion, specific findings on EEG, and improvement with withdrawal of the drug. Fatal outcomes have been reported.^{5,6} Early and prompt recognition of the condition is crucial for the prevention of its morbidity and mortality.

The mainstay of treatment is prompt withdrawal of antibiotics and symptomatic treatment with benzodiazepines or barbiturates. Very severe cases with refractory seizures have been treated with hemodialysis. Phenytoin should be avoided as a treatment of this condition due to its lack of GABA-agonist activity.

Conclusion

Cefepime can cause NCSE, predominantly in patients with renal dysfunction. Its frequency is probably underestimated in hospitalized patients with multiple comorbid conditions. Hospitalists should be aware of this unusual but critical relationship, especially in patients with renal failure. A high level of clinical suspicion and an emergency EEG are essential to obtain a prompt and accurate diagnosis.

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References

1. Wallace KL. Antibiotic-induced convulsions. *Crit Care Clin.* 1997;13:741-762.
2. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. *Pharmacotherapy.* 2006;26(8):1169-1174.
3. De Sarro A, Ammendola D, Zappala M, Grasso S, De Sarro GB. Relationship between structure and convulsant properties of some β -lactams antibiotics following intracerebroventricular microinjections in rats. *Antimicrob Agents Chemother.* 1995;39:232-237.
4. Capparelli FJ, Diaz ME, Hlavnicka A, Wainsztein NA, Leiguarda R, Del Castillo ME. Cefepime- and cefixime-induced encephalopathy in a patient with normal renal function. *Neurology.* 2005;65(11):1840.
5. Chatellier D, Jourdain M, Mangalaboyi J, et al. Cefepime induced neurotoxicity: an underestimated complication of antibiotherapy in patients with acute renal failure. *Intensive Care Med.* 2002;28:214-217.
6. Maganti R, Jolin D, Rishi D, Biswas A. Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. *Epilepsy Behav.* 2006;8(1):312-314.
7. Martínez-Rodríguez JE, Barriga FJ, Santamaria J, et al. Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure. *Am J Med.* 2001;111(2):115-119.
8. Sugimoto M, Uchida I, Mashimo T, et al. Evidence for the involvement of GABA(A) receptor blockade in convulsions induced by cephalosporins. *Neuropharmacology.* 2003;45(3):304-314.
9. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30(2):239-245.