CLINICAL VIGNETTE

Cefepime-Induced Neurotoxicity in a High Risk Patient

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Introduction

Cefepime is a preferred agent for broad spectrum antibiotic coverage. While it is generally well tolerated, there is increasing evidence to suggest associated neurotoxicity. Here we present a case of cefepime-induced neurotoxicity in a patient with end stage renal disease on hemodialysis and multiple neurologic diagnoses, including prior stroke, seizure disorder, and cognitive deficits. This case highlights pertinent risk factors for cefepime neurotoxicity, including renal insufficiency and neurologic disease, and illustrates the limitations of cefepime dose adjustments in preventing neurotoxic side effects.

Case Report

A 79-year-old male with end stage renal disease on hemodialysis was brought to the emergency department by his wife due to 12 hours of aphasia and confusion, which began when he awoke that morning. Review of systems was otherwise negative with no recent trauma, no additional new focal neurologic deficits, and no suggestion of new infection. He had had hemodialysis the day prior without any complications.

Two weeks prior to presentation, he had been admitted to another hospital for fevers. He was found to have *Pseudomonas* bacteremia with no clear source despite comprehensive workup, and was discharged with a prolonged outpatient course of intravenous tobramycin. His case was reviewed by the outpatient Infectious Disease one week prior to his current presentation, and his tobramycin was switched to cefepime due to concerns for ototoxicity. He was recommended a four-week course of cefepime 2 grams intravenously three times a week after hemodialysis. He received two doses of cefepime in the days preceding his current presentation, with his last dose one day prior to presentation.

The patient's medical history was notable for type 2 diabetes mellitus, hyperlipidemia, hypertension, history of cerebrovascular accidents with mild residual left sided weakness and facial paralysis, prior alcohol use disorder with history of delirium tremens, history of possible post-hemodialysis seizures, and mild cognitive impairment. His medications included repaglinide and atorvastatin. The patient's exam on presentation was notable for an encephalopathic state in which he was awake but inattentive, oriented to self only, intermittently following simple commands, and inappropriately answering questions with "yes" or "no" responses. There was slight left nasolabial fold flattening, left arm weakness, and possible left leg weakness which was difficult to ascertain due to his mental status. Labs showed no leukocytosis or electrolyte disturbances; his createnine of 6.66mg/dL and elevated blood urea nitrogen (BUN) were at baseline for the patient. He had mildly elevated transaminases. Urinalysis, TSH, folate, vitamin B12, thiamine, HIV, RPR were normal. Imaging, including CT of the head and brain MRI/MRA revealed no acute intracranial pathology, but re-demonstrated known areas of infarct at the left inferior cerebellum, right basal ganglia, and right caudate head. Neurology was consulted in the emergency department as there was a high suspicion for stroke, central nervous system (CNS) infection, or seizure. They recommended further evaluation with lumbar puncture, electroencephalogram (EEG), and initiation of levetiracetam for seizure prophylaxis. The patient was admitted to the general medicine service for further evaluation.

On hospital day 2, the patient became increasingly sedated and developed new left upper extremity myoclonic jerks. EEG showed continuous generalized slowing and 2-3 Hz generalized sharp waves, suggestive of nonconvulsive status epilepticus (NCSE). The patient was transferred to the ICU for monitoring and started on additional antiepileptics with lacosamide and topiramate. Infectious Disease and Neurology had high clinical suspicion for cefepime neurotoxicity and recommended deferring further invasive testing, such as lumbar puncture. The patient was initially transitioned to meropenem due to concerns for cefepime neurotoxicity, however once the EEG showed NCSE, he was switched to ceftazidime given meropenem's ability to lower the seizure threshold. He additionally underwent three consecutive days of hemodialysis, continued antiepileptic therapy, and continuous EEG monitoring. On hospital day 4, EEG showed resolution of NCSE, his mental status improved, and his myoclonic activity resolved. During the remainder of his admission, the patient continued thrice weekly hemodialysis, antiepileptic therapy, and ceftazidime for his previous *Pseudomonas* bacteremia. His mental status continued to improve, though never fully recovered to his original baseline at time of discharge one month later.

Discussion

Cefepime is a fourth-generation cephalosporin with activity against Gram-positive and Gram-negative organisms, including *Pseudomonas aeruginosa* and resistant *Enterobacteriacae*.[1] It is a preferred parenteral agent in critically ill patients requiring broad spectrum antimicrobial coverage. While cefepime is

generally well tolerated,[1] cefepime neurotoxicity has become an increasingly recognized clinical entity through several documented case reports.[2-8]

Cefepime neurotoxicity is a clinical syndrome characterized by a wide spectrum of neurologic manifestations, including reduced consciousness, disorientation, aphasia, myoclonus, seizures, and NCSE.[9-11] These symptoms are typically accompanied by abnormal EEG findings, such as diffuse slow wave delta activity, and triphasic sharp waves.[9-11] Cefepime neurotoxicity occurs more often in elderly patients (mean age of 67) with time to symptom onset of 4-5 days after initiating therapy.[9-11] Treatment includes discontinuation of the drug, initiating antiepileptic therapy, and, if indicated, hemodialysis.[9-11] Cefepime is easily dialyzable with removal of 70% of a given dose in a three-hour hemodialysis session.[12] Pharmacokinetic studies have demonstrated clinical utility of at least one hemodialysis session in the treatment of cefepime neurotoxicity due to its ability to dramatically lower serum cefepime levels.[13] There are case series that suggest overall improvement in clinical outcomes with initiation of hemodialysis in patients with severe neurotoxic symptoms, such as coma or NCSE.[14] Continuation of maintenance hemodialysis in ESRD patients also shortens recovery time neurotoxicity.[7] The adverse effect is felt to be due to the antibiotic's gamma-aminobutyric acid (GABA) antagonist properties, Antiepileptic drugs with GABA agonist activity are therefore preferred in treating neurotoxicity.[9-10] However, agents without strong GABA activity, such as levetiracetam and lacosamide, were used in this patient with adequate resolution of his NCSE and neurologic symptoms. With appropriate therapies, clinical improvement can be seen within 2 days, with most patients achieving full or partial symptom resolution.[9-11]

Renal insufficiency is a well-documented risk factor for developing cefepime neurotoxicity.[7-11] Cefepime is excreted primarily by the kidneys,[15] thus putting patients with reduced renal function at risk for higher circulating drug levels in the blood as well as the cerebrospinal fluid (CSF) as the antibiotic is able to cross the blood brain barrier.[7-11] Of the reported cefepime neurotoxicity cases, 80-87% occur in patients with renal disease[9-10] with one prospective cohort study citing a 1 in 6 incidence rate of neurotoxicity in patients with glomerular filtration rate (GFR) < 15 mL/min/ m^2.[8] Based on increasing numbers of case reports, the FDA released a drug safety communication in 2012 advising clinicians to make appropriate dose adjustments in patients with renal insufficiency.[16]

While most neurotoxicity cases occur due to cefepime doses that are excessive for the patient's renal function, there is literature demonstrating that neurotoxicity can occur despite appropriate dose adjustments.[3,7,9-10] This patient was recommended renally-dosed cefepime 2 grams three times a week after hemodialysis. In long term hemodialysis patients, this regimen was found to yield drug levels above the minimal inhibitory concentration for most target pathogens, resulting in adequate treatment of gram negative bacteria.[17,18] Although one study demonstrated no significant adverse events with this regime, it is unclear whether the study included neurotoxicity in their analysis.[18]

While there is no established toxic serum threshold for cefepime, groups have suggested that serum levels > 22 mg/L[19] or trough levels > 20 mg/L may be associated with higher risk of neurotoxicity.[20] The previously discussed renally-dosed regimen of 2 grams three times weekly results in mean trough level of 23.3 mg/L,[17] which falls in the serum drug range associated with higher risk of neurotoxicity.[19-20] In light of this conflicting evidence, it may be prudent to reevaluate the cefepime dosing regimen currently recommended for hemodialysis patients.[17-18]

An additional risk factor for cefepime neurotoxicity is premorbid CNS disease.[7,21-23] The mechanism of toxicity is thought to be due to concentration-dependent GABA antagonism enabled by cefepime's ability to cross the blood brain barrier.[24,25] Cefepime neurotoxicity has been seen in patients with seizure disorder and other CNS diseases including cerebrovascular disease, encephalitis, spina bifida, and dementia.[10,22-23] Retrospective cohort studies have demonstrated that premorbid CNS disease may increase the risk of cefepime neurotoxicity.[7,21] However, there is a gap in the literature as to which CNS diseases have a higher propensity for being associated with the adverse effect. Nonetheless, this information may be useful to practitioners in identifying high-risk patients and selecting appropriate antibiotic regimens.

The patient cited in the case report represents the stereotypical presentation of cefepime neurotoxicity. However, using Naranjo criteria to assess for drug associated adverse reactions, cefepime-induced neurotoxicity was calculated, at best, as "probable" in explaining his clinical presentation.[26] There were two main limitations in the analysis: lack of CSF evaluation and lack of serum cefepime levels to demonstrate toxicity. The clinical suspicion for cefepime neurotoxicity was so high however, based on the available information at presentation, that CSF sampling was not deemed necessary. Additionally, no serum or CSF cefepime levels were obtained in this patient. However,the drug level cutoffs for determining toxicity are currently ill-defined, making such data points potentially difficult to interpret. Further research to define what constitutes an effective, yet safe serum drug level is required.

Conclusion

Drug related adverse reactions are a common occurrence in clinical medicine. This case report hopes to bring to attention an increasingly recognized adverse effect of cefepime: neurotoxicity. Renal insufficiency is a notable risk factor for cefepime neurotoxicity, however as our case illustrates, this adverse effect still occurred despite preventative measures such as appropriate renal dose adjustment and regular hemodialysis. This suggests our patient faced other contributing factors to his neurotoxicity, such as his premorbid CNS disease. Treatment should include drug dose adjustment or discontinuation,[9-10] hemodialysis to promptly reduce serum cefepime levels,[13] and antiepileptic therapy.[9-10] Overall, cefepime should be used with

caution in high-risk patients and clinical symptoms should be monitored closely with a low threshold to consider drug-related neurotoxicity in the setting of new, neurologic changes.

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