CLINICAL VIGNETTE

Cefepime Induced Neurotoxicity

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Case

An 85-year-old female with a past medical history of hypothyroidism and hypertension was brought into the emergency department by family for altered mental status. Per the patient's daughter, the patient felt weak for three days leading up to admission. On the day of admission, she was not responding appropriately to questions, and was brought in for further evaluation. At baseline, the patient was independent in activities of daily living, able to drive, and do her own shopping. Per the family, the patient denied any other complaints or symptoms during the days leading up to admission.

On arrival to the emergency department, the patient's vitals were temperature 35.8, blood pressure 132/80, heart rate 95, respiratory rate 18, and pulse oximetry of 99% on room air. Her physical exam was notable for the patient being oriented only to self, not responding appropriately to questions, but able to move all extremities equally. The patient also had suprapubic tenderness to palpation. The remainder of the physical exam was unremarkable. Her laboratory data revealed a white blood cell count of 12.08, hemoglobin of 11.5, and platelets of 338. Basic metabolic panel was notable for sodium of 134 and creatinine of 0.73, while the remainder was normal. Liver chemistries tests were within normal limits. Urinalysis was concerning for infection with +3 leukocyte esterase and 199 white blood cells per high power field. Chest x-ray was negative for acute findings.

Given the initial presentation, vitals, and laboratory findings, the suspected diagnosis was septic encephalopathy secondary to a urinary tract infection. The patient was started on cefepime given her history of multi-drug-resistant bacterial organisms during prior admissions. The patient's mental status initially improved close to baseline after receiving fluids and antibiotics; however, on hospital day 2, the patient noted visual hallucinations and worsening mental status. CT scan of the brain was unremarkable. Given concern for cefepime induced neurotoxicity, the patient was transitioned to piperacillin-tazobactam per infectious disease recommendations. Neurology was consulted and recommended an MRI brain and electroencephalogram (EEG) due to persistent altered mental status. MRI brain was negative for acute findings. EEG demonstrated left temporal intermittent slowing, which was seen on a prior EEG two years before her current admission, and rare sharp waves, which could suggest a lower seizure threshold. Lumbar puncture was also performed and cerebrospinal fluid studies were unremarkable. Over the course of the hospitalization, the patient's mental status improved and hallucinations resolved with treatment of urinary tract infection and discontinuation of cefepime. Cefepime was added to her allergy list.

Discussion

Cefepime, a fourth-generation cephalosporin antibiotic, has been reported to cause neurotoxic adverse events in many case reports and retrospective reviews. Cefepime is generally used in the inpatient setting to treat a variety of infections given its broad spectrum coverage. The incidence of cefepime induced neurotoxicity (CIN) has been reported to range between 1 and 15%.[1] Early recognition of signs and symptoms of CIN is critical to treatment and management. Delays in diagnosis may be due to clinicians being unaware of the adverse effects of cefepime. As symptoms of CIN can overlap with other disease processes, EEG studies can be helpful in early detection of CIN.[1]

Cefepime induced neurotoxicity is thought to be related to enhanced affinity of cefepime to GABA receptors, thereby creating competitive antagonism with endogenous GABA.[2,3] About 10% of serum cefepime can cross the blood brain barrier, though this can be higher with blood brain barrier dysfunction.[2] Cefepime is excreted primarily by the kidneys, which is why kidney dysfunction can lead to greater serum concentrations. Greater serum concentrations can lead to a lower seizure threshold and increase neuronal excitability by blocking the effects of GABA.[1] Patients are at higher risk of CIN when cefepime dosing is not adjusted for creatinine clearance, though CIN has also been reported in patients with normal creatinine clearance. Kidney disease, as well as inflammatory conditions, can also cause disruption to the blood brain barrier and increased central nervous system concentrations of cefepime.[2] Other risk factors for CIN include critical illness, older age, liver disease, and pre-existing neurologic condition.[3]

Cefepime induced neurotoxicity (CIN) can present in a variety of ways. Symptoms of CIN include altered mental status, reduced consciousness, aphasia, seizures, myoclonic activity of the limbs, agitation, and coma.[2, 3] Due to symptom overlap with other diagnoses and lack of awareness, median interval between onset of symptoms and diagnosis for CIN was 5 days in one retrospective review.[4] In Payne et al, a systematic review of literature including 135 patients, neurotoxicity was recognized within a median of 4 days after initiation of cefepime. Electro-

encephalography (EEG) abnormalities included nonconvulsive status epilepticus, myoclonic status epilepticus, triphasic waves, and focal sharp waves.[2] A retrospective review was completed in a tertiary care medical center on 42 patients who developed encephalopathy after cefepime initiation.[1] CIN was diagnosed if patients developed neurologic symptoms (mental status changes, seizures, myoclonus) after cefepime initiation, clear temporal association of neurologic symptoms with cefepime initiation, and clinical or EEG improvement after discontinuation of cefepime. EEG abnormalities observed in these patients included nonconvulsive status epilepticus, generalized periodic discharge, generalized rhythmic delta activity and generalized spike and wave pattern.

Treatment of cefepime induced neurotoxicity includes discontinuation, decrease in dosage, initiation of antiepileptic agents, and hemodialysis.[2] In all patients, but particularly in the elderly, it is important to calculate creatinine clearance and adjust dosing of cefepime as needed prior to initiation. As Payne et al discussed previously, clinical improvement was seen in a median of 2 days post intervention.[2] Complete resolution of symptoms was seen in 50% of patients and partial resolution in 39%. In our patient discussed above, improvement in symptoms was seen 3 days after discontinuation of cefepime with complete resolution of symptoms prior to discharge.

In summary, cefepime induced neurotoxicity can present as a wide range of neurologic symptoms. Awareness of the presenting signs and symptoms of CIN is critical in diagnosis. Clinicians should have a higher index of suspicion for CIN in patients with kidney disease, older age, critical illness, and pre-existing neurologic conditions. For patients with kidney disease, cefepime dosing should be adjusted based on creatinine clearance as elevated serum concentrations increase risk for CIN. EEG can be helpful in early diagnosis as most patients with CIN exhibit abnormal EEG findings.[1] Prompt diagnosis can aid in an earlier intervention and reversal of CIN symptoms.

REFERENCES

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