A Curious Case of Confusion: Cefepime-Induced Encephalopathy

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CEFEPIME-INDUCED ENCEPHALOPATHY

RISK FACTORS

- Renal impairment
- High cefepime doses
- Prolonged therapy
- Older age

PATHOPHYSIOLOGY

- Reduced cefepime clearance
- Accumulation in the central nervous system
- Impaired GABA neurotransmission

CLINICAL PRESENTATION

- Altered mental status
- Myoclonus
- Seizures
- Aphasia

DIAGNOSIS AND MANAGEMENT

- Discontinue cefepime
- Supportive care

Clinical Case

- A 94-year-old male with past medical history including coronary artery disease, chronic kidney disease stage 3, and dementia, originally presented to the emergency department for confusion. Prior to this presentation, the patient had previous admissions to an outside hospital system, where the patient was found to be positive for bacteremia. At the outside hospital system, the patient was started on antibiotic therapy with cefepime and was continued on outpatient cefepime therapy after discharge. The patient re-presented to the outside hospital for lethargy, and the patient was discharged on cefepime and metronidazole for continued management of bacteremia. Family reported that while at home, the patient had increasing rigidity to the point where the patient would not attempt to stand up, could not put a drinking straw into his mouth, and had increasing daytime somnolence. Family also reported occasional facial muscle jerking. In addition, family stated that throughout the patient's duration of antibiotic therapy, the patient had persistent worsening of confusion, deterioration of alertness, and decrease of overall activity level. Prior to being diagnosed with bacteremia, the patient was able to independently complete dressing, bathing, and light housework activities. After approximately 7 days from his discharge from the outside hospital, the patient presented to this hospital for confusion.

- Initial workup was negative for leukocytosis, negative for electrolyte abnormality, negative for thyroid function abnormality, urinalysis found to be non-concerning for infection, normal toxicology screen, negative respiratory viral panel, but workup was notable for increased creatinine from baseline. Initial CT of the head and subsequent MRI of the brain were both negative for an acute intracranial process. After hospital admission, geriatric medicine inpatient consultation was placed for confusion. Initial assessment from consultation reported concerns for cefepime-induced encephalopathy with recommendations to modify the antibiotic regiment from cefepime. Infectious disease was also consulted, who noted that given the patient presented with decreased creatinine clearance, the patient likely had systemic accumulation of cefepime. The patient's antibiotic regiment was modified to from cefepime to piperacillin-tazobactam. After approximately 48 to 72 hours off of cefepime, the patient started to speak with family, walk with assistance, and started to complete other activities of daily living with his baseline level of assistance.

Literature Review/ Evidence

- Cefepime is a fourth-generation cephalosporin antibiotic that is commonly used to treat both gram-positive and gram-negative infections. The primary mechanism of cefepime-induced encephalopathy (also referenced to in current medical literature as cefepime-induced neurotoxicity) is hypothesized to be associated with cefepime's ability to cross the blood-brain barrier. Accumulation of cefepime can lead to concentration-dependent competitive inhibition of gamma-aminobutyric acid (GABA) receptors. This impairment of the main inhibitory neurotransmitter system in the brain results in central nervous system hyperexcitation- presenting clinically as encephalopathy and additional neurologic manifestations.

- In large retrospective cohorts of hospitalized adults, the incidence of cefepime-induced encephalopathy is estimated to be in the range of 4-7% among those receiving cefepime therapy, although exact incidence is unknown. Current literature has established age as an independent risk factor for developing symptoms of cefepime neurotoxicity. Another key risk factor for development of cefepime-induced encephalopathy includes decreased renal function given the antibiotic is primarily excreted by the renal system. While the risk of developing cefepime-induced encephalopathy does increase in a dose-dependent manner, neurotoxicity can occur even with renal-based medication adjustments and can occur also in cases with normal renal function.

- Additional established risk factors for developing cefepime-induced encephalopathy include pre-existing central nervous system disease (including stroke, dementia, epilepsy, etc.), critical illness, hypertension, and diabetes. Most cases are reversible after discontinuation of cefepime, while utilization of hemodialysis also exists as an option for management in refractory cases. In addition to encephalopathy, additional presentations that may be attributed to the neurotoxic effects of cefepime include myoclonus, seizures, and aphasia.

Unique Aspects of Case

- In the practice of inpatient geriatric medicine, consultations requesting evaluation for older adults presenting with altered mental status are common. When assessing older adults with altered mental status it is important to maintain an appropriately broad differential, taking into account all key clinical information.

- While cefepime-induced encephalopathy does have a low incidence, it is important to consider this possibility in the appropriate clinical context as failure to appropriately treat neurotoxicity related to the use of cefepime can result in significant morbidity and mortality.

Recommendations

- In the absence of alternative identifiable sources for altered mental status, medical providers should maintain a high level of suspicion for a drug-induced encephalopathy in any patient whose clinical course has included treatment involving cefepime, particularly among those with risk factors for cefepime-induced encephalopathy.

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