Kentucky Antimicrobial Stewardship Innovation Consortium

Educational Pearl

Cefepime-Induced Neurotoxicity

Cefepime is a fourth-generation cephalosporin with broad spectrum activity against gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa*. While all beta-lactam antibiotics have the potential to cause neurotoxicity, particular focus has been on cefepime.[1] Who is at risk for developing cefepime-induced neurotoxicity? Can it be prevented?

Symptoms of Cefepime-Induced Neurotoxicity

Symptom onset has been reported to occur within four days after the initiation of cefepime and primarily consists of altered mental status and decreased consciousness. Myoclonus and nonconvulsive status epilepticus have been observed with symptom progression.[2]

Incidence of Cefepime-Induced Neurotoxicity

Cefepime-induced neurotoxicity (CIN) is most commonly reported to occur in critically ill patients, where altered mental status and encephalopathy is already common, making attribution to cefepime difficult. Reported incidence of CIN varies widely across multiple studies which may be due to differences in patient characteristics and endpoint definitions. In one study of critically ill patients receiving cefepime, CIN occurred in 15% of patients.[3] Conversely, another study of critically ill patients who received cefepime, piperacillin-tazobactam, or meropenem, beta-lactam-associated neurotoxicity occurred in 2% – 3% of patients.[4]

Risk Factors for Developing Cefepime-Induced Neurotoxicity

Most cases of suspected or confirmed CIN have been reported to occur when doses were not appropriately adjusted for renal impairment. However, CIN has also been reported in patients with normal renal function and those receiving appropriate doses.[3-6] Conditions that alter the blood-brain barrier integrity, such as sepsis, central nervous system (CNS) infections, and previous brain injury, may increase the penetration of cefepime into the CNS from 10% to 45%[4] and predispose patients to develop neurotoxicity.

Management of Cefepime-Induced Neurotoxicity

Discontinuation of cefepime has been reported to improve symptoms within two days.[2] Anticonvulsants are not warranted unless convulsive seizures or nonconvulsive status epilepticus are present. In patients with life-threatening symptoms, hemodialysis can reduce the elimination half-life and accelerate recovery.[5]

Prevention of Cefepime-Induced Neurotoxicity

Renal dose adjustments for cefepime are recommended when creatinine clearance is ≤ 60 ml/min.[6] Renal function should be monitored and symptoms of neurotoxicity should be assessed regularly in high-risk patients.[5] There is evidence to suggest a threshold concentration for toxicity[2] which may be mitigated by alternative cefepime dosing strategies like extended or continuous infusions.

Key Takeaway: Multiple potential causes of altered mental status are often present in patients receiving cefepime, making identification of cefepime-induced neurotoxicity difficult. Renal impairment and critical illness are risk factors. Adjusting cefepime doses in renal impairment is key to prevention and primary treatment is cefepime discontinuation.

References

1. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Ninth Edition. Chapter 21. *Cephalosporins*.
2. Payne, LE, Gagnon DJ, Riker RR, et al. Cefepime-induced neurotoxicity: a systematic review. Crit Care. 2017;21(1):276. doi: 10.1186/s13054-017-1856-1.
3. Fugate JE, Kalimullah EA, Hocker SE, et al. Cefepime neurotoxicity in the intensive care unit: a cause of severe, underappreciated encephalopathy. *Crit Care*. 2013 Nov 7;17(6):R264.
4. Haddad NA, Schreier DJ, Fugate JE, et al. Incidence and predictive factors associated with beta-lactam neurotoxicity in the critically ill: A retrospective cohort study. *Neurocrit Care*. 2022 Aug;37(1):73-80. doi: 10.1007/s12028-022-01442-1.
5. Lee SJ. Cefepime-Induced Neurotoxicity. *J Neurocrit Care.* 2019;12(2):74-84. https://doi.org/10.18700/jnc.190109
6. Package insert. Cefepime. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050679s036lbl.pdf.

Created 8.22.23