CLINICAL VIGNETTE

Cefepime-induced Encephalopathy and Neurotoxicity

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Case Report

An 88-year-old male with end-stage renal disease on peritoneal dialysis was hospitalized for worsening peripheral vascular disease with gangrenous foot. He underwent left below the knee amputation. Post-operative course was complicated by atrial fibrillation with rapid ventricular rate, hospital acquired pneumonia and worsening delirium. The patient was started on renally dosed vancomycin and cefepime for pneumonia and sepsis. He also continued to receive peritoneal dialysis, but with a different frequency of sessions per nephrology. The patient remained intermittently delirious during his hospitalization, and progressively became more tremulous. He eventually developed myoclonic jerks that would last for several seconds, every few minutes. He had no history of seizures or other neurologic processes or history of brain injuries. He also became increasingly more encephalopathic, and developed myoclonic seizures involving his face, limbs and trunk, eventually causing status epilepticus and urgent ICU transfer. EEG showed waves consistent with non-convulsive status epilepticus, and he required acute stabilization with benzodiazepines and anti-epileptic drugs. On further evaluation, serum and cerebral spinal fluid concentrations of cefepime were elevated and it was concluded that patient likely had cefepime-induced neurotoxicity. Antibiotics were discontinued, anti-epileptic administration continued, and more frequent dialysis sessions were required to stabilize the patient. He eventually improved with resolution of the myoclonic movements and no further episodes of seizure activity were observed. His mentation eventually returned close to his baseline and he was discharged to a skilled nursing facility for further recovery.

Discussion

This case illustrates an example of cefepime-associated encephalopathy from neurotoxicity. Cefepime is a fourth-generation cephalosporin widely used for the treatment of severe bacterial infections. Similar to other cephalosporins, cefepime is largely excreted via the kidneys. The neurotoxic effects from this antibiotic was first reported in 1999 on dialysis patients.[1] In 2002, the Food and Drug Administration (FDA) adjusted the labeling to account for increased risk of encephalopathy, seizures and myoclonus, especially in the setting renal dysfunction.[2] The mechanism was thought to be attributed to the drug's ability to cross the blood-brain barrier, causing concentration dependent competitive ϒ-aminobutyric acid (GABA) antagonism.[3] The accumulation of cefepime levels is often related to decreased clearance from reduced glomerular filtration in renal failure or increased CNS penetration from blood brain barrier (BBB) dysfunction. Therefore, it is strongly advised to dose-adjust cefepime in those with reduced creatinine clearance and monitor those with impaired renal function to avoid toxicities.[3]

Additionally, there is increased risk of neurotoxic symptoms in ICU patients as the critically ill are more prone to disruptions in the BBB from systemic inflammation, causing toxic levels in the blood and CNS. Approximately 10% of cefepime crosses the BBB, but acute illness and poor nutrition causing renal impairment and poor protein binding, can increase the transfer to 45%.[4]

Neurologic complications of cefepime induced encephalopathy have been reported from 1-10 days (average 5 days) after initiation of the antibiotic. Symptoms may include altered mental status, involuntary movements, seizures, and more severe sequelae including status epilepticus, coma or even death.[5,6] Symptoms may improve within 2-7 days after cessation of the drug, and prompt drug clearance may be warranted in those with end stage renal disease.[6] Patients with underlying neurologic disorders may be at greater risk for developing neurotoxicity.[7] Diagnosis is often made clinically with neurologic symptoms correlated with initiation of cefepime, accompanying EEG abnormalities and symptoms resolving after discontinuation of the drug. It is also important to rule of other reversible causes of toxic or metabolic encephalopathy. Elevated CSF/blood ratio of cefepime if available can support the diagnosis.[8]

One single-center retrospective study of hospitalized patients treated with dose-adjusted cefepime between 2012-2016, reviewed the risk of cefepime induced encephalopathy on end-stage renal disease patients.[8] In 422 patients, six developed cefepime related toxicity with a higher incidence of 7.5% patients with renal dysfunction, particularly ESRD, despite renal dose adjustment for creatinine clearance. Among these patients, toxicity developed even at the lowest dose of 0.5gm/day. Other risk factors included advanced age, liver disease and pre-existing neurologic or CNS conditions.[7]

A systemic review of cefepime related toxicity included studies published from 1980 to 2016.[9] They identified 135 cases with median age of 69 years. Eighty percent had renal dysfunction and all patients exhibited some level of altered mental status.

The most common symptoms were reduced consciousness (47%), myoclonic activity (42%), and confusion (42%). Seventy-three percent of the cohort demonstrated EEG abnormalities, with the most common being non-convulsive status epilepticus, triphasic waves, and focal sharp waves. This review of cefepime neurotoxicity was the first to describe the range of symptoms. The neurologic complications may include altered mentation, impaired consciousness, myoclonic movements and seizures, aphasia and in severe cases, even coma or death. Treatment involves cessation of the antibiotic, prompt clearance of the drug if concerned for renal toxicity, and supportive care for the symptoms and maintenance of hemodynamic stability.

Although pre-existing comorbidities such as renal dysfunction and neurologic disease may increase the risk, cefepime induced encephalopathy has also been reported in those with normal renal function and no co-morbid diseases.[10] Cases of cefepime-associated neurotoxicity in patients with normal renal function, resolved after discontinuation of the antibiotics. This report included asynchronous myoclonus and expressive aphasia as adverse effects.[11]

Abnormal epileptiform discharges and EEG activity on many patients with normal renal function receiving cefepime. These examples illustrate how neurotoxicity may be an underreported or hidden side effect cefepime, especially in those with normal renal function. Perhaps this increased risk reflects enhanced affinity for the GABA receptor due to specific molecular conformations of the drug. Alternatively, cefepime may exhibit chemical structural affinity for increased accumulation in spinal fluid.

While caution should be taken regarding this potential risk of the antibiotic, this should be balanced with the severity of the infection and any need for appropriate treatment. For example, a higher dose may be warranted in a case of severe infection such as febrile neutropenia whereas a lower dose may be preferred in less severe infections when taking precautions to avoid cefepime induced encephalopathy.

In 2012, the FDA issued a Safety Warning reminding the need to adjust cefepime dosage based on renal function.[12] The statement referenced 59 cases of non-convulsive status epilepticus reported in the FDA's Adverse Event Reporting System database between 1996 and 2012.

Conclusion

Cefepime is a widely used antibiotic for more severe infections such as hospital-acquired pneumonia, soft tissue infections and intra-abdominal infections. Complications of encephalopathy and neurotoxicity have been associated with the drug, especially in elderly patients with renal dysfunction, although complications can also occur with preserved renal function.

The above case and summary of literature review report the full spectrum of sequelae resulting from cefepime-related neurotoxicity. Awareness of the risk factors leading to this condition and judicious use of antibiotics are crucial in preventing further complications. Additional investigation of studies with a larger sample size is needed to allow for more robust analyses. Increased vigilance, careful review of comorbidities and safer dose-adjustment strategies are necessary to reduce risk of cefepime induced encephalopathy.

REFERENCES

1. **Wong KM, Chan WK, Chan YH, Li CS**. Cefepime-related neurotoxicity in a haemodialysis patient. *Nephrol Dial Transplant*. 1999 Sep;14(9):2265-6. doi: 10.1093/ndt/14.9.2265. PMID: 10489256.
2. **Bazan JA, Martin SI, Kaye KM**. Newer beta-lactam antibiotics: doripenem, ceftobiprole, ceftaroline, and cefepime. *Med Clin North Am*. 2011 Jul;95(4):743-60, viii. doi: 10.1016/j.mcna.2011.03.009. PMID: 21679790.
3. **Khorasani-Zadeh A, Greca I, Gada K**. Cefepime-Induced Seizures: The Overlooked Outpatient Adverse Reaction. *Cureus*. 2020 Jul 19;12(7):e9268. doi: 10.7759/cureus.9268. PMID: 32699729; PMCID: PMC7372227.
4. **Durand-Maugard C, Lemaire-Hurtel AS, Gras-Champel V, Hary L, Maizel J, Prud'homme-Bernardy A, Andréjak C, Andréjak M**. Blood and CSF monitoring of cefepime-induced neurotoxicity: nine case reports. *J Antimicrob Chemother*. 2012 May;67(5):1297-9. doi: 10.1093/jac/dks012. Epub 2012 Jan 31. PMID: 22298349.
5. **Kenzaka T, Matsumoto M**. Cefepime-induced encephalopathy. *BMJ Case Rep*. 2018 Feb 21;2018: bcr2017223954. doi: 10.1136/bcr-2017-223954. PMID: 29467125; PMCID: PMC5847961.
6. **Dakdouki GK, Al-Awar GN**. Cefepime-induced encephalopathy. *Int J Infect Dis*. 2004 Jan;8(1):59-61. doi: 10.1016/j.ijid.2003.09.003. PMID: 14690782.
7. **Grill MF, Maganti RK**. Neurotoxic effects associated with antibiotic use: management considerations. *Br J Clin Pharmacol*. 2011 Sep;72(3):381-93. doi: 10.1111/j.1365-2125.2011.03991.x. PMID: 21501212; PMCID: PMC3175508.
8. **Nakagawa R, Sato K, Uesaka Y, Mitsuki T, Kondo K, Wake A, Ubara Y, Kanzaki M.** Cefepime-induced encephalopathy in end-stage renal disease patients. *J Neurol Sci*. 2017 May 15;376:123-128. doi: 10.1016/j.jns.2017.03.018. Epub 2017 Mar 16. PMID: 28431597.
9. **Payne LE, Gagnon DJ, Riker RR, Seder DB, Glisic EK, Morris JG, Fraser GL**. Cefepime-induced neurotoxicity: a systematic review. *Crit Care*. 2017 Nov 14;21(1):276. doi: 10.1186/s13054-017-1856-1. PMID: 29137682; PMCID: PMC5686900.
10. **Meillier A, Rahimian D**. Cefepime-induced encephalopathy with normal renal function. *Oxf Med Case Reports*. 2016 Jun 1;2016(6):118-20. doi: 10.1093/omcr/omw042. PMID: 27274853; PMCID: PMC4887827.
11. **Isitan C, Ferree A, Hohler AD**. Cefepime induced neurotoxicity: A case series and review of the literature. *eNeurologicalSci*. 2017 Aug 4;8:40-43. doi: 10.1016/

j.ensci.2017.08.001. PMID: 29260037; PMCID: PMC5730896.
12. **Brooks M**. FDA Issues Safety Reminder on Cefepime. Available at: https://www.medscape.com/viewarticle/766390.