CLINICAL VIGNETTE

Cefepime-induced Neurotoxicity Treated with a Benzodiazepine

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Introduction

Neurotoxicity associated with the recent use of the fourth-generation cephalosporin cefepime can present in a variety of ways, from confusion to myoclonus to status epilepticus, particularly in patients with underlying chronic renal disease.[1] Although the first line treatment is to discontinue the medication, additional treatment may be indicated if recovery to baseline mental status is not achieved. We describe a case of cefepime-induced neurotoxicity treated with the benzodiazepine lorazepam.

Case

A 67-year-old male was brought to the emergency department from his skilled nursing facility due to altered mental status. His past medical history includes chronic urinary retention with post-obstructive chronic kidney disease requiring suprapubic catheter, hypertension, COPD, and opioid use disorder on chronic methadone. The nursing facility staff and the patient's family reported he was hospitalized at an outside hospital one week prior for septic shock in the setting of Methicillin-Resistant Staphylococcus aureu pneumonia and Vancomycin-Resistant Enterococcus urosepsis. At that hospitalization, the patient was at his baseline mental status, alert, and oriented to self, place, date, and situation, and he was verbal. He was treated with several antibiotics but discharged to the skilled nursing facility to complete a course of linezolid for MRSA pneumonia. The day after discharge to the skilled nursing facility, the staff at the nursing facility noted that the patient was non-verbal, less responsive, and refused to take his oral medications. Given the acute change in mental status, he was sent to the emergency department for further evaluation.

In the emergency department, the patient's vital signs included temperature 36.6°C, HR 98/min, BP 140/82, respiratory rate 14 breaths per minute, and oxygen saturation of 98% on ambient air. On physical exam he was awake but non-verbal, and would not respond to orientation questions nor follow any verbal commands. Exam was remarkable for myoclonus in all four extremities, without evidence of hemiparesis. Laboratory tests included white blood cell count of 5.9, hemoglobin 10.4 g/dL, platelet count 189, sodium 141 mmol/L, potassium 4.6 mmol/L, chloride 109 mmol/L, bicarbonate 19 mmol/L, blood urea nitrogen 46 mg/dL, creatinine 5.68 mg/dL, and glucose 97 mg/dL. His initial urine toxicology screen was positive for benzodiazepine, opiates, and methadone. Urinalysis revealed elevated white blood cells, leukocyte esterase, and nitrites. His vitamin B12 level was 288 pg/mL, and he was started on supplementation. Initial CT Head without contrast was negative for any acute intracranial pathology. He was given one dose of cefepime and vancomycin in the emergency department for empirical coverage for possible sepsis. The patient did not have suprapubic discomfort on exam but Urology exchanged the suprapubic catheter in the emergency department given the positive urinalysis. The patient was admitted to the hospitalist service for further evaluation and management.

The patient was switched from vancomycin back to linezolid as this was what he was previously receiving for treatment of MRSA pneumonia. However, his QTc on telemetry monitoring was elevated to 639 after 48 hours and he was switched to renally-dosed vancomycin. Urine culture grew vancomycin-resistant enterococcus, which he had previously grown at the outside facility. Infectious Diseases recommended continuing the vancomycin, and thought the VRE in the urine was likely colonization. Given the patient's persistent altered mentation and myoclonus noted on exam, MRI brain did not reveal any acute intracranial pathology. Neurology was consulted for further guidance on evaluation of patient's persistent encephalopathy and myoclonus. Electroencephalography revealed diffuse slowing, but did not reveal any seizure activity. Neurology believed the patient had some type of toxic encephalopathy related to recent administration of cefepime, versus less likely serotonin syndrome due to the interaction between linezolid and methadone. Given the patient did not have febrile episodes, agitation, diaphoresis, or any other hemodynamic instability, serotonin syndrome was deemed less likely. A lumbar puncture was obtained and was not suggestive of an infectious or inflammatory process.

Further records were assessed from the outside hospital where the patient was previously admitted. The patient had received high-doses of cefepime for empiric treatment of septic shock, and these doses were not renally dosed. Thus, the patient's altered mental status was more likely due to cefepime-induced neurotoxicity, though cessation of cefepime had not yet improved the encephalopathy. Neurology recommended treatment with scheduled benzodiazepine as there were several case reports of treatment with these agents. The patient was given lorazepam 0.5mg twice a day, and after 24 hours, he began to follow more commands and he also began to speak. He was able to state that the last thing he remembered was being discharged to the skilled nursing facility, but he could not recall the events

afterward. He also shared that in addition to chronic methadone, he also took scheduled clonazepam for anxiety disorder, which explained the appearance of benzodiazepine on his initial urine toxicology screen. This was not listed on the patient's medication list at the skilled nursing facility. The patient's mental status continued to recover back to his baseline, and he was discharged back to his skilled nursing facility.

Discussion

Cefepime-induced neurotoxicity is thought to be due to the antibiotic crossing the blood-brain barrier and inhibiting the release of gamma-aminobutyric acid (GABA), which results in hyperexcitation of neurons.[2] Though more cases were associated with the administration of higher doses of cefepime, there have been cases of neurotoxicity documented in patients with chronic kidney disease who receive renally-dosed cefepime.[3] Cefepime-induced neurotoxicity tends to appear about four days after initiation of cefepime. There is a wide range of neurologic symptoms, including confusion, agitation, myoclonus, and seizures including status epilepticus.

Treatment of cefepime-induced neurotoxicity begins with discontinuing the antibiotic. This alone can lead to a recovery to baseline mental status in one to three days. However, in more severe cases where the neurologic symptoms have not resolved, further treatment may be indicated. Hemodialysis can rapidly clear cefepime. One meta-analysis reported the median time to recovery after hemodialysis was one day.[4] Anticonvulsant medications, such as the benzodiazepine lorazepam, have also been used, particularly if seizures or status epilepticus are present, with recovery to baseline mental status. Because benzodiazepines bind to GABA receptors and increase the release of GABA, they are thought to counteract the inhibitory effect of cefepime. In our case though, the patient did not have evidence of seizure activity on EEG,[5] he responded to the administration of lorazepam, with resolution of myoclonus and encephalopathy. It is possible that this particular patient may have experienced a component of benzodiazepine withdrawal since he was previously on scheduled clonazepam. However, the time course of his symptoms appeared to be too prolonged to be explained by withdrawal alone. Thus, benzodiazepines should be considered as additional treatment for cefepime-induced neurotoxicity, particularly if cessation of cefepime alone does not lead to recovery of baseline mental status.

Conclusion

Cefepime-induced neurotoxicity is an important adverse effect of this antibiotic, particularly in patients with underlying chronic renal insufficiency. Even with dosage adjustments in renal impairment, there is still elevated risk for neurotoxicity. It is important to identify this early and promptly discontinue this medication. Other treatments, including hemodialysis and the use of benzodiazepines, should be considered if patient does not improve with discontinuation of the antibiotic alone.

REFERENCES

1. **Fugate JE, Kalimullah EA, Hocker SE, Clark SL, Wijdicks EF, Rabinstein AA**. Cefepime neurotoxicity in the intensive care unit: a cause of severe, underappreciated encephalopathy. *Crit Care*. 2013 Nov 7;17(6):R264. doi: 10.1186/cc13094. PMID: 24200036; PMCID: PMC4057506.
2. **Saini T, Gaines MN, Sohal A, Li L**. Cefepime-Induced Neurotoxicity. *Cureus*. 2021 Sep 8;13(9):e17831. doi: 10.7759/cureus.17831. PMID: 34660040; PMCID: PMC8502754.
3. **Lee SJ**. Cefepime-induced neurotoxicity. *J Neurocrit Care*. 2019 Dec 24:12(2):74-84. [Internet] Available at: https://www.e-jnc.org/journal/view.php?doi=10.18700/jnc.190109.
4. **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.
5. **Wanleenuwat P, Suntharampillai N, Iwanowski P**. Antibiotic-induced epileptic seizures: mechanisms of action and clinical considerations. *Seizure*. 2020 Oct;81:167-174. doi: 10.1016/j.seizure.2020.08.012. Epub 2020 Aug 14. PMID: 32827980.