

CASE REPORT

Neurotoxicity after intrathecal cefepime administration: case report

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Cefepime is a fourth-generation cephalosporin and beta-lactam antibiotic that is generally well tolerated, but there are reports of neurotoxicity proposed to result from competitive antagonism of γ -aminobutyric acid (GABA) receptors. A 10-year-old male with a past medical history of severe traumatic brain injury requiring decompressive craniotomy and cranioplasty with subsequent persistent cerebrospinal fluid (CSF) leak was admitted for scheduled lumbar drain placement and transmastoid repair with ossiculoplasty. Surgery was performed with no complications, and he was admitted to the pediatric intensive care unit (PICU). In the PICU, the patient was inadvertently administered 50.54 mg/kg cefepime intrathecally via the lumbar drain. He immediately developed pruritus of his lower back and gluteal region, emesis, and muscle spasms to his lower extremities and then progressed to status epilepticus. The patient was endotracheally intubated and administered IV lorazepam, midazolam, levetiracetam, propofol, and fosphenytoin. Medical toxicology was consulted and recommended pentobarbital bolus and infusion. Initial cerebrospinal fluid (CSF) and serum cefepime concentrations were 760.6 mg/L and 6.3 mg/L, respectively. CSF exchange was discussed by medical toxicology and neurosurgery but was deemed too high risk by neurosurgery. In lieu of CSF exchange, hemodialysis was recommended by medical toxicology to increase the CSF-plasma cefepime concentration gradient. After two days, serum cefepime concentrations were undetectable, and CSF concentrations had decreased to 89.4 mg/L. After seven days, cefepime was undetectable in CSF. Our case report is the first documented incident of iatrogenic neurotoxicity from the intrathecal administration of cefepime resulting in immediate neurotoxicity with an extremely high CSF cefepime concentration of 760.6 mg/L and serum level of 6.3 mg/L, in contrast to previous reports of toxicity at serum levels as low as 35 mg/L and 22 mg/L and CSF levels of 6-18 mg/L.

Introduction

Cefepime, a fourth-generation cephalosporin and beta-lactam antibiotic, is widely used in medicine to treat both gram-positive and gram-negative bacterial infections. Although cefepime is generally well tolerated, there are reports of neurotoxicity, described as encephalopathy, hallucinations, myoclonus, seizures, and stroke-like symptoms in critically ill patients.¹ The proposed mechanism is that once across the blood brain barrier, cefepime

competitively antagonizes γ -aminobutyric acid (GABA)-A receptors in the central nervous system (CNS).^{2,3} We report a case of iatrogenic cefepime neurotoxicity after accidental intrathecal administration.

Case Presentation

A 10-year-old male with a past medical history of severe traumatic brain injury requiring decompressive craniotomy and cranioplasty with subsequent persistent cerebrospinal fluid (CSF) leak from the right ear was admitted for scheduled lumbar drain placement and transmastoid repair with ossiculoplasty and right tympanostomy tube placement. Surgery was performed with no complications, and he was admitted to the pediatric intensive care unit (PICU). In the PICU, the patient was inadvertently administered 50.54 mg/kg cefepime intrathecally via the lumbar drain. He immediately developed pruritus of his lower back and gluteal region, emesis, and significant pain and muscle spasms to his lower extremities. Shortly following the initial symptoms, he displayed seizure-like convulsions, hypoxia, and became unconscious. The patient was endotracheally intubated and administered IV lorazepam, midazolam, levetiracetam, propofol, and fosphenytoin. Emergent CT head was unremarkable. Medical toxicology was consulted and recommended pentobarbital bolus and infusion. 27 mL of CSF was removed via the lumbar drain. Pentobarbital, propofol, and midazolam infusions were continued due to continued seizure activity and continuous electroencephalogram (cEEG) with frequent epileptiform discharges concerning for status epilepticus. CSF exchange was discussed by medical toxicology and neurosurgery but was deemed too high risk by neurosurgery due to the patient's condition and recent surgery. In lieu of CSF exchange, hemodialysis was recommended by medical toxicology to increase the CSF-plasma cefepime concentration gradient. Initial CSF and serum cefepime concentrations were 760.6 mg/L and 6.3 mg/L, respectively. Hemodialysis was initiated, and the patient was kept on cEEG monitoring.

After two days, serum cefepime concentrations were undetectable and CSF concentrations had decreased to 89.4 mg/L. After initial high-flux hemodialysis, the patient was continued on continuous veno-venous hemofiltration (CVVH) for four days. Anti-seizure medications and sedatives were gradually weaned without evidence of breakthrough seizure. After seven days, cefepime was undetectable in CSF. The patient remained seizure-free on levetiracetam, perampanel, and phenobarbital. The patient was extubated after nine days and continued to improve. He was transferred out of the intensive care unit on day 16 post-event and discharged on day 29 at his neurological baseline.

Discussion: All beta-lactams are not uniformly neurotoxic, but cephalosporins and penicillins are associated with significant neurotoxicity and should not be given intrathecally.³ Since intrathecal cefepime is not routinely administered, we report a rare case of neurotoxicity from intrathecal

cefepime administration resulting in immediate neurotoxicity along with CSF and serum cefepime concentrations. Cefepime induced neurotoxicity (CIN) has been previously well-described in the peer-reviewed medical literature in patients receiving intravenous cefepime. A recent review identified 37 publications representing 135 patients from 19 single-case reports, 9 case series, 8 retrospective cohort studies, and a single prospective cohort trial.¹ Reported signs and symptoms of CIN include encephalopathy, myoclonus, seizures, and aphasia. Risk factors for CIN are proposed to lead to toxic CSF cefepime concentrations and include advanced age, renal dysfunction, comorbid critical illness, excessive dosing, and an altered blood-brain barrier due to inflammatory conditions, organic acid accumulation, and previously mentioned renal dysfunction. Symptom onset typically occurs around 4 days after the initiation of intravenous cefepime therapy. Treatment of CIN consists of discontinuing cefepime therapy, administering anti-seizure medications and/or benzodiazepines for neuroexcitation and seizures, and hemodialysis. Clinical improvement typically occurs within two days; however, permanent injury and death have been reported. CIN has been associated with serum cefepime trough concentrations greater than 35 mg/L,⁴ while others have suggested a lower serum concentration of 22 mg/L may be predictive of neurotoxicity.⁵ CSF concentrations have only been reported in four patients with cefepime-induced neurotoxicity,⁶⁻⁸ ranging from 6 – 18 mg/L with a median of 13 mg/L.

In contrast to previous reports of cefepime-induced neurotoxicity, this patient's symptom onset was immediate and progressed rapidly from localized pruritis to status epilepticus. The patient gradually improved with aggressive anti-seizure therapy (including benzodiazepines and barbiturates), mechanical ventilation, and hemodialysis. Compared to previously reported cases of CIN, our patient had a protracted clinical course lasting 29 days, most likely the result of the extremely high CSF cefepime concentration. CSF cefepime concentrations significantly decreased but remained toxic despite 2 days of hemodialysis and CVVH. While clinical factors and expert opinion precluded the use of a CSF exchange in our patient due to excessive risk, it should be strongly considered after the intrathecal administration of neurotoxic xenobiotics. CSF exchange has been reported to prevent neurotoxicity after the intrathecal administration of methotrexate⁹ and increase CSF clearance of intrathecally administered cytarabine.¹⁰

Note

This case report was previously presented at the Annual Scientific Meeting of the American College of Medical Toxicology in April 2025 as an abstract. However, this submission is much longer, with more discussion of the case and literature to contribute to the understanding of this pathology.

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