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Cefepime Neurotoxicity in an Adolescent Cystic Fibrosis Patient with Aminoglycoside-Induced Acute Kidney Injury

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Objective: To describe a case of cefepime neurotoxicity in an adolescent with cystic fibrosis and aminoglycoside-associated acute kidney injury (AKI).

Case Summary: A 15-year-old, 46-kg male with cystic fibrosis (CF) and chronic sinusitis was admitted to the hospital for CF exacerbation. The patient was subsequently discharged to complete home antibiotic therapy with intravenous gentamicin and cefepime. Thirteen days after discharge, while still receiving intravenous antibiotics, the patient presented to an outside hospital complaining of vomiting, fatigue, decreased appetite, and decreased urine output. The patient was diagnosed with AKI and was transferred to our institution, where he displayed signs and symptoms consistent with encephalopathy. Encephalopathy was thought to be consistent with cefepime-associated neurotoxicity. After 2 hemodialysis sessions, the encephalopathy resolved. Over the course of admission, the patient's renal function improved

Discussion: This patient experienced neurotoxicity thought to be secondary to cefepime in the setting of AKI. Aminoglycoside therapy most likely led to the AKI. We believe that our patient represents the fourth pediatric patient with cefepime-associated encephalopathy described in the literature and the second without chronic renal dysfunction.

Conclusions: Children receiving cefepime should be monitored for AKI. In the presence of AKI, cefepime
doses may need to be adjusted and the patient should be monitored for signs and symptoms of neurotoxicity.

Cefepime is an optimal empiric antibacterial for many infectious processes because of its broad spectrum of activity. It has good penetration into lung tissue and the central nervous system (CNS) and is effective against methicillin- susceptible *Staphylococcus aureus* (MSSA) and *Pseudomonas aeruginosa* infections.**1** Cefepime is commonly used in children and adolescents with cystic fibrosis (CF) exacerbations for directed therapy against MSSA and *P. aeruginosa* infections.**2** Additionally, cefepime possesses a mild adverse effect profile, causing rash in only 4%, diarrhea in 3%, and headache in 1% of patients at its highest recommended dose (2 g every 8 hours).**3**

Neurotoxicity, including encephalopathy, myoclonus, and seizures, has been associated with cefepime through postmarketing surveillance.**4-6** Most of these cases involved the elderly or patients with prior renal dysfunction. In a patient with normal renal function, it appears unlikely that cefepime, when administered at the recommended dose and interval, would contribute to these reported neurologic effects. Neurotoxicity has been reported rarely in patients with normal renal function.**6** Aminoglycosides are often used in patients with CF and are well-recognized nephrotoxins. Prolonged aminoglycoside exposure and repeated aminoglycoside courses can increase the risk of acute kidney injury (AKI).**7** To our knowledge, only 3 cases of cefepime-related neurotoxicity in adolescent patients have been reported in the literature. We report an additional case of cefepime neurotoxicity in an adolescent with CF and aminoglycoside-associated AKI.

Case Report

A 15-year-old, 46-kg male with a past medical history of CF and chronic sinusitis was admitted to the hospital for persistent upper respiratory tract infection over the 2 weeks prior to admission and worsening pulmonary function tests during the year prior to admission. The patient was empirically started on intravenous vancomycin and high-dose (11 mg/kg) extended-interval intravenous tobramycin. Tobramycin concentrations were obtained after the second dose. During this first admission, 2- and 6-hour postdose concentrations were 19.4 mg/L and 3.6 mg/L, respectively, corresponding to estimated clearance to undetectable serum concentrations 13-15 hours postdose. The patient's serum creatinine at the time was 0.75 mg/dL.

Lower respiratory cultures contained MSSA and *Stenotrophomonas maltophilia*, with past cultures significant for *P. aeruginosa*. Antibiotic therapy was subsequently changed to intravenous cefepime and intravenous gentamicin, based on susceptibility data. On the fourth hospital day, the patient was discharged home on intravenous cefepime 2 g every 8 hours, intravenous gentamicin 500 mg (11 mg/kg) every 24 hours, and oral sulfamethoxazole/ trimethoprim 800/160 mg every 12 hours. Seven days after discharge, a gentamicin concentration obtained mid-interval was 7.8 mg/L and serum creatinine was 1 mg/dL. The single mid-interval concentration was difficult to interpret since it was not a pre- or postdose; however, it most likely represented a decreased gentamicin clearance, particularly in the presence of a 33% increase from baseline in serum creatinine. No action was taken.

Thirteen days after discharge, the patient presented to an outside hospital with a chief complaint of nausea and vomiting. He reported increased fatigue and decreased appetite over the previous 2 days and no urine output over the past 24 hours. Symptoms were unrelieved by any intervention. No fever, diarrhea, pain, or shortness of breath was noted. Physical examination was generally unremarkable. No motor or sensory deficits were noted and the patient was alert and oriented to person, place, and time. Chest and abdominal radiographs were performed and displayed no acute disease. Laboratory tests revealed aspartate aminotransferase 386 units/L, alanine aminotransferase 276 units/L, alkaline phosphatase 185 units/L, and a white blood cell count of 16,500/μL, with 83% neutrophils. Serum creatinine was 10.5 mg/dL, blood urea nitrogen was 69 mg/dL, and a random gentamicin concentration was 39.2 mg/L. Cefepime and gentamicin, which the patient had been receiving since his previous admission, were discontinued. Electrolytes and all other laboratory parameters were within normal limits. The patient was treated with a normal saline bolus and infusion and was transferred to our hospital, a pediatric teaching facility where the patient receives the majority of his care, for further management.

Upon arrival at the hospital, the patient was noted to be sleepy and poorly responsive but arousable, with some intermittent confusion and combativeness. At this time the patient's plasma ammonia concentration was slightly elevated at 85.2 μg/dL. He became increasingly confused and combative and was subsequently transferred to the intensive care unit (ICU). Upon arrival at the ICU, he responded only to painful stimuli and intermittently to commands. No nystagmus or myoclonus was observed. Metabolic encephalopathy secondary to cefepime neurotoxicity with AKI was suspected.

The patient subsequently underwent hemodialysis for 2.5 hours. His gentamicin concentration prior to the first hemodialysis session was 32.4 mg/L; at the end of the first 2.5-hour session the gentamicin concentration had declined to 18.4 mg/L. There was no clinical evidence of seizures but the patient required intubation. The patient had another hemodialysis session approximately 10 hours later. An electroencephalogram (EEG) was not obtained due to extubation of the patient; a neurologic exam was negative and he exhibited marked clinical improvement.

Over the 9 days following this second hospital admission, the patient received 7 additional hemodialysis sessions (Table 1). Gentamicin concentrations are illustrated in Figure 1. Eight days after the patient's last dose of gentamicin and 7 days following the second admission, his gentamicin concentration had decreased to 1.6 mg/L. At this time the serum creatinine level was 5.25 mg/dL, electrolytes were within normal limits, and urine output was appropriate. Encephalopathy was completely resolved, with mental status at baseline, although the patient did not remember the few days surrounding this episode. Seventeen days after the second hospital admission, the patient was discharged home with a serum creatinine level of 1.9 mg/dL. At a 2-week follow-up clinic visit, the patient was recovering well, with a serum creatinine level of 0.94 mg/dL.

Discussion

This patient experienced neurotoxicity thought to be secondary to cefepime in the setting of AKI. The observed reaction was possibly due to cefepime, according to the Naranjo adverse reaction probability scale.**8** A rechallenge was not completed under the same clinical conditions for clear reasons. It is our belief that the most likely cause of encephalopathy was cefepime, as similar neurologic findings have been described in patients receiving regular doses of cefepime in the face of severe renal insufficiency.**4,6,9** No other explanation for the symptoms was found. Unfortunately, cefepime serum concentrations were not available in this case.

Table 1. Hemodialysis Sessions During Admission

DAYS POSTADMISSION	HEMODIALYSIS (HOURS)
1	5.5
2	4
3	4
4	4
5	4
6	4
7	4

AKI was the most likely event leading to the accumulation of cefepime. The pathogenesis of AKI could have been multifactorial, but it is likely that aminoglycoside therapy played a dominant role. Aminoglycosides are known to cause acute tubular necrosis, which may occur as early as 5 days after treatment initiation.**4,10** Risk of aminoglycoside nephrotoxicity increases when therapy lasts longer than 5 days, with persistent drug exposure, with consistently elevated

trough serum concentrations, when used with other nephrotoxins, and in the setting of prior renal insufficiency. Patients with CF may be at increased risk for aminoglycoside- related nephrotoxicity because of the likelihood that they will receive repeated courses of aminoglycosides throughout the course of the disease.**7**

Other medications may have contributed to the patient's AKI. While precipitation in acidic urine is less common with the newer sulfonamide antibiotics, a high percentage of acetylated sulfamethoxazole, a relatively insoluble form of the drug, is found in the urine. These crystalline deposits can lead to urinary obstruction.**11** Cephalosporins have also been associated with nephrotoxicity, although to a lesser degree than aminoglycosides, and occasionally secondary to interstitial nephritis.**12,13** Cephalosporins have been shown to act synergistically with aminoglycosides to produce nephrotoxicity.**10,14** Dehydration may also have been a contributing factor to the AKI.

High daily doses of cefepime may accumulate in the presence of impaired renal function and lead to neurotoxicity. Neurotoxicity secondary to cefepime has been reported widely in the literature, mostly in patients with impaired renal function.**4-6** Cefepime is eliminated approximately 85% unchanged in the urine; therefore, dosage must be adjusted in patients with renal dysfunction or those undergoing renal replacement therapy.**15** It is frequently used to treat CNS infections, because of its ability to cross the blood-brain barrier, but this quality also predisposes to neurotoxicity.**6** In AKI, organic acids compete for active transport out of the CNS, causing further increased cerebral concentrations.**16** In the CNS, cefepime (similar to other β-lactam antibacterials) antagonizes γ-aminobutyric acid, disrupting its inhibitory actions in the CNS and subsequently leading to increased excitatory neurotransmitter action.**6** This lowers the seizure threshold and may contribute to other neurotoxic effects as well.**17,18**

In the event of cefepime accumulation, the drug can be removed by hemodialysis. It has been shown that a 3-hour hemodialysis session removes 68% of cefepime present in the body.**15** Our patient received 2.5 hours of emergent hemodialysis due to AKI to decrease complications seen from either cefepime or uremia and to prevent aminoglycoside-associated ototoxicity. Time to onset of symptoms of cefepime neurotoxicity can be highly variable. In a report of 5 cases of cefepime-induced encephalopathy, 2 patients also received aminoglycosides and experienced acute renal failure.**16** In these patients, symptoms occurred 12 and 16 days after initiation of cefepime therapy. Reported events most commonly include confusion and temporal-spatial disorientation, as well as encephalopathy, myoclonus, nonconvulsive status epilepticus, seizures, coma, and even death. In one retrospective review of 54 patients with cephalosporin-associated neurotoxicity, 93% of patients with cefepime neurotoxicity displayed confusion as a chief symptom, with 29% of patients displaying subsequent myoclonus. **4** Patients were an average of 61 years old, and 12% experienced AKI at the time of cefepime toxicity.

To our knowledge, our patient represents only the fourth pediatric patient with cefepime-associated encephalopathy to be described in the literature and only the second with normal renal function at baseline. Alpay and colleagues described a 15-year-old male who was receiving continuous ambulatory peritoneal dialysis due to endstage renal disease, as well as cefepime.**19** Subsequently, he presented with memory problems and difficulty reading, writing, and walking. This episode was associated with nonconvulsive status epilepticus discovered upon EEG.

A 15-year-old female with a history of end-stage renal disease receiving chronic hemodialysis experienced lethargy, confusion, and myoclonic jerks that the authors attributed to cefepime therapy.**20** In the case most similar to ours, Chatellier and colleagues reported that a 16 year-old male receiving cefepime, sulfamethoxazole/trimethoprim, azithromycin, and tobramycin for CF exacerbation had no previous renal dysfunction.**16** This patient suffered status epilepticus and coma but experienced a complete recovery.

As in our patient, early recognition, cefepime discontinuation, and hemodialysis may prevent agitation, confusion, and disorientation from progressing to myoclonus, status epilepticus, coma, and death. Children, particularly those with preexisting renal dysfunction or receiving concomitant aminoglycosides, should be monitored closely for signs and symptoms of neurotoxicity while receiving cefepime. It is clear that careful monitoring and dosage adjustment of cefepime are necessary to prevent accumulation leading to complications.**15** As cefepime becomes increasingly standard treatment for CF exacerbations because of its activity against *P. aeruginosa* and emergence of antimicrobial resistance, practitioners should be aware of this potential adverse effect.

Our adolescent patient experienced AKI and encephalopathy while receiving intravenous gentamicin and cefepime. History of events and patient presentation were highly suggestive of neurotoxicity secondary to cefepime. To our knowledge, our experience is only the second case in which a pediatric patient with normal baseline renal function experienced neurotoxicity thought to be associated with cefepime. However, our patient's symptoms differed from those in the previously reported case in that seizures and coma were not present. Two of the now 4 reported cases of cefepime-related neurotoxicity in adolescents have occurred in patients with CF, and special attention is warranted due to use of high antimicrobial doses and frequency of concomitant aminoglycoside use in this population.

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