Clinical Case Reports

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CASE REPORT

Cefepime-induced neurotoxicity in a pediatric patient on chronic hemodialysis: a case report

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Key Clinical Message

Impaired renal function increases the risk for cefepime-induced neurotoxicity. Symptoms include disorientation, myoclonus, status epilepticus, ataxia, gait disturbance, coma, and death. A high index of suspicion and early recognition of symptoms can minimize the risk of progression of symptoms to permanent neurologic impairment or death.

Keywords

Cefepime, hemodialysis, neurotoxicity, pediatric, renal.

Background

Cefepime is a fourth-generation cephalosporin used to treat serious infections with multidrug-resistant organisms. Cefepime is primarily (85%) cleared by the kidney, and drug toxicity can occur in patients with both acute and chronic renal impairment. Adverse neurologic effects due to cefepime were previously reported to be mild (insomnia, dizziness) and uncommon (3% in the general population) [1]. Multiple cases of serious neurotoxicity in the setting of renal dysfunction have been described in adults [2, 3]; however, we identified only two reported cases in children [4, 5]. Here, we describe a novel case of cefepime-induced neurotoxicity in a pediatric patient with end-stage renal disease (ESRD) on chronic hemodialysis.

Case Report

A 7-year-old male with anuric ESRD was admitted for treatment of Enterobacter cloacae bacteremia. He had ESRD since birth due to bilateral congenitally dysplastic kidneys and required chronic hemodialysis. His medical history included pulmonary hypoplasia with severe chronic lung disease, failure of peritoneal dialysis due to recurrent infections, and developmental delay. He was initially empirically treated with ceftriaxone for 3 days and clinically improved, but repeat blood cultures grew Enterobacter cloacae resistant to ceftriaxone yet susceptible to cefepime.

Following these results, ceftriaxone was stopped, and cefepime was started at 400 mg intravenous every 24 h (50 mg/kg/dose) with the dose given immediately following dialysis on hemodialysis days [6]. The patient continued hemodialysis as per his usual chronic dialysis schedule, in the mornings on days 1, 3, 5, and 8 of cefepime. On day 3 of cefepime, the patient's mother perceived leg weakness and mild, intermittent loss of balance, which was attributed to deconditioning. Two days later, he fell from a seated position in his hemodialysis chair just before starting dialysis. There were no

significant changes to his volume status or electrolytes at that time. On day 7 of cefepime, he fell while walking. His bedside nurse noted that he "looked like a drunk man walking" and physical therapist noted that he would "sway slightly on anterior/posterior toes [with] limited eccentric control."

On day 8 of cefepime, patient was noted to have disorientation to person and place and severe truncal ataxia with inability to walk independently. He had racheting flexion movements of the head and trunk as well as a brief episode of unilateral hand tremor within 15 min of starting a hemodialysis treatment. The dialysis treatment was stopped early. He was normotensive and not tachycardic. Electrolytes at that time showed sodium 141 mEq/L, potassium 4.2 mEq/L, chloride 100 mEq/L, bicarbonate 22 mEq/L, creatinine 6.7 mg/dL, blood urea nitrogen 134 mg/dL, total calcium 9.8 mg/dL, albumin 3.4 g/dL, and phosphorus 4.5 mg/dL. Plasma cefepime concentration level was not obtained, as this testing is not available at our hospital. Computerized tomography scan of the head and lumbar puncture were ordered to be completed with general anesthesia, but symptoms resolved before they were completed; the studies were canceled as it was determined that the risks of the procedures far outweighed any potential benefit. Electroencephalogram showed generalized spike and wave pattern lasting up to 7 sec, interpreted as consistent with underlying ESRD.

His symptoms were more pronounced immediately before he was due for hemodialysis and most severe on a Monday (day 8) after not receiving hemodialysis through the weekend. Symptoms were concerning for cefepime-induced neurotoxicity; therefore, cefepime was discontinued after the 8th dose. Within 24 h of cefepime cessation, the symptoms resolved completely and he reverted back to his baseline neurological function. He was oriented, conversant, and ambulated without difficulty. He completed treatment of Enterobacter cloacae bacteremia with meropenem and continues to do well on chronic hemodialysis.

Discussion

An acute neurological changes in uremic patients have a wide differential of potential causes including metabolic encephalopathy, drug toxicity, infection, hypertensive encephalopathy, and intracranial pathology [4, 7]. Drug-induced neurotoxicity should be considered if there are acute neurologic changes, and the patient is receiving cefepime. Symptoms are progressive and can include disorientation, myoclonus, nonconvulsive status epilepticus, coma, and death [2, 3]. In contrast to previously reported adult cases, pediatric patients on dialysis manifest additional symptoms of ataxia and gait disturbance [4]. The latency period can vary, but symptoms occur most often with a latency period of 5 days after initiation of cefepime [3, 8]. Resolution of symptoms after stopping cefepime is strongly suggestive of the diagnosis. In some cases, symptoms are permanent or progressive despite removal of the offending agent [3, 8, 9].

The proposed mechanism of the neurotoxic effects of beta-lactam antibiotics is via γ-aminobutyric acid (GABA), an inhibitory neurotransmitter [10]. Cephalosporins competitively inhibit the binding of GABA to GABA-A receptors, producing a hyperexcitatory state that may lead to seizures or other neurologic effects [11]. Decreased renal clearance of the drug results in higher serum levels and an increased risk for GABA-mediated effects. In addition, the toxic organic acids that are present in the cerebral spinal fluid (CSF) of patients with renal failure can competitively inhibit active transport of the drug out of the CSF into the blood, which can exacerbate the neurologic effects caused by high serum levels alone.

A retrospective study of thirty patients with febrile neutropenia found that those with cefepime-associated neurologic toxicity had a higher median cefepime trough level than those without neurologic toxicity (28 mg/L, compared to 7.2 mg/L, $P < 0.001$) [9]. A multivariate analysis showed that the cefepime trough level was independently associated with an increased risk for neurotoxicity, and a logistic regression model suggested that at a level of 22 mg/L, the risk of neurologic toxicity was 50%. Plasma levels of cefepime are not routinely used in usual clinical care but may play a role when there is a concern for adverse effects.

Cefepime is cleared by first-order pharmacokinetics at a rate of 120 mL/min in healthy adult patients, and approximately 85% of the drug is cleared unchanged by the kidneys [6]. The half-life of cefepime is approximately 2.3 h in patients with normal renal function, but if the creatinine clearance is <10 mL/min, the half-life is approximately five times longer [8, 12].

Unpredictable cefepime levels can result from acute changes in the volume of distribution via capillary leak syndrome, hypoalbuminemia, or volume overload [9, 13].

This could explain why cefepime-induced neurotoxicity has occurred in some patients despite appropriately adjusted dosing regimens for the level of renal impairment[9]. Routine monitoring of cefepime plasma concentrations may be helpful in patients with renal impairment to minimize the risk of drug toxicity.

In 2012, the U.S. Food and Drug Administration released a postmarket safety announcement regarding importance of dose adjustment in patients with a creatinine clearance of <60 mL/min [14]. However, there are no pediatric-specific dose adjustments, and

recommendations for children have been extrapolated from pharmacokinetic data in adults. Due to the prolonged half-life in the setting of renal impairment, thrice weekly dosing (mean dose 33.2 mg/kg) has been proposed for long-term hemodialysis patients without residual renal function. Pharmacokinetic studies in hemodialysis patients show that thrice weekly postdialysis dosing results in adequate antimicrobial efficacy and improved patient compliance [15]. A three-hour session of high-flux hemodialysis is reported to remove 68% of the total amount of cefepime present in the blood at the start of the hemodialysis session [6, 15].

Both pediatric and adult patients with impaired renal function are at increased risk for cefepime-induced neurotoxicity. A high index of suspicion and early recognition of symptoms can minimize the risk of progression of symptoms to permanent neurologic impairment or death if the drug is stopped immediately. If available, monitoring of cefepime plasma concentration levels may be helpful in preventing the development of neurotoxicity and could also aid in making a timely diagnosis once symptoms develop.

Authorship

MGL: participated in patient management, collected and analyzed the data, and wrote the manuscript. SA: participated in patient management and data collection and contributed to drafting the initial manuscript. JAS, RDS, and SB: contributed to the interpretation of the case and critically reviewed the manuscript. JPS: participated in patient management, collected and analyzed the data, and critically reviewed the manuscript. All authors approved the final manuscript as submitted.

Conflicts of Interest

None declared.

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