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Cefepime related status epilepticus

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Cefepime is a fourth-generation cephalosporin β-lactam antibiotic. Neurotoxic effects of cefepime include slurred speech, tremor, encephalopathy and seizures. Presented herein are two cases of a 7-year-old boy and 16-year-old girl who developed cefepime-related neurotoxicity. The first patient who had uncontrolled epilepsy was stable for 1 month while on ketogenic diet, when he developed convulsive status epilepticus following two doses of cefepime initiated for cellulitis. The second patient that had undergone an arteriovenous fistula after being placed on a hemodialysis program for chronic renal failure was administered cefepime for an infection at the site of the fistula. On the third day of antibiotic treatment, she developed non-convulsive status epilepticus. The second patient was a typical case of cefepime-related neurotoxicity due to renal failure. To the best of our knowledge, convulsive status epilepticus has not been reported before in association with cefepime treatment, which underlines the significance of our first cases.

Keywords: cefepime; status epilepticus; neurotoxicity syndromes; ketogenic diet; seizures

INTRODUCTION

Cefepime is a fourth-generation β-lactam cephalosporin with activity against both gram-positive and gram-negative bacteria (1). Compared to third-generation cephalosporins, cefepime is better tolerated, with a lower incidence of anaphylaxis, seizures, neutropenia and bleeding episodes (1). Approximately 85% of the drug is cleared unchanged by the kidneys, and dose adjustment is recommended in patients with creatinine clearance <60 mL/min (1, 2)

The known neurotoxic effects of beta-lactam antibiotics, particularly carbapenems and penicillins, include slurred speech, tremor, encephalopathy and seizures (2). Patients with renal failure and an underlying epileptic disorder are more prone to the toxic effects of cephalosporins (3). Previously reported cases of cefepime-related status epilepticus (SE) have been associated with non-convulsive status epilepticus (NCSE) in adult patients with renal failure because of unadjusted dosing (4-6).

We present two pediatric cases; the first patient had uncontrolled epilepsy who developed convulsive SE after receiving two doses of cefepime, although renal function was normal. The second patient was on hemodialysis program despite a renal transplant. Although the patient did not have a previous history of epilepsy, she developed NCSE following initiation of cefepime treatment for a catheter infection. Additionally, we discuss the dose-dependent or independent epileptogenic effects of cefepime in children.

Case Report 1

A 7-year-old boy was referred to our hospital with a 2-month history of uncontrolled seizures. He had initially been treated with phenytoin, followed by the addition of phenobarbital, clonazepam and then levetiracetam, without success. He still suffered 15-20 seizures/day. He had generalized tonic-clonic seizures lasting for 1-3 minutes and SE twice in the last month before hospital admission.

Neurological examination and laboratory workup were normal. The patient's epileptic seizures continued despite successive addition of valproic acid, lamotrigine and clobazam to his treatment regimen, which prompted initiation of midazolam infusion. When this measure also failed to keep the seizures under control, the patient was switched to ketogenic diet, on the third day of which the frequency of his

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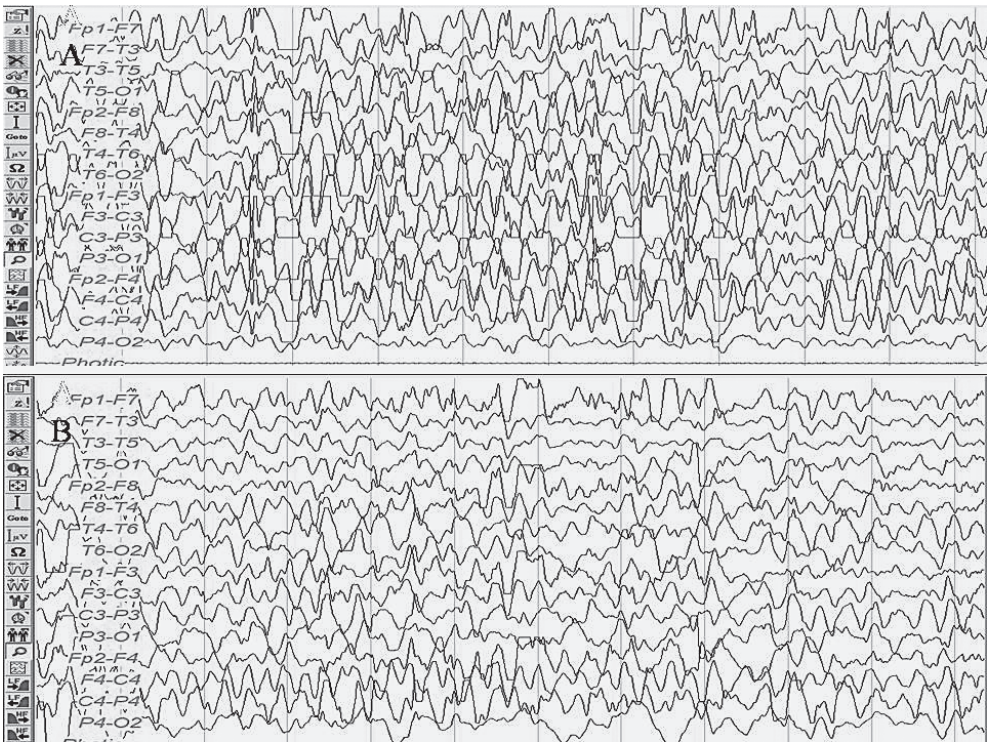

FIGURE 1. **Ictal electroencephalogram (EEG) obtained during seizures in case 1 (A); interictal EEG pattern after diazepam administration (B) (amplitude 200 μv, low filter 1 Hz, high filter 35 Hz).**

seizures decreased and by the tenth day the seizures ceased completely. Midazolam infusion, phenytoin, levetiracetam and clonazepam were discontinued and the patient was maintained on a combination of valproic acid, lamotrigine, clobazam and phenobarbital, under which his condition remained stable.

The patient was seizure-free for 30 days following initiation of ketogenic diet. However, after receiving two doses of cefepime (50 mg/kg *i.v.* q12 h) for cellulitis that developed at the site of a previous intravenous catheter, he developed a generalized tonic-clonic seizure, which recurred every 30 minutes without regaining consciousness in-between. Results of the laboratory examinations were within the normal limits except for high blood glucose (205 mg/dL). The electroencephalogram (EEG) obtained during one of the seizures is depicted in Figure 1. After 2 initial boluses of diazepam 15 minutes apart, continuous infusion was started. Considering cefepime as a possible cause, the drug was discontinued. The patient's seizures ceased on the second day on diazepam infusion, which was subsequently stopped. After a seizure-free month as an inpatient, he was eventually discharged.

Case Report 2

A 16-year-old girl who had undergone renal transplantation a year before for chronic renal failure due to nephrolithiasis related to hyperoxaluria, presented to the emergency department with cough and nasal discharge. She was on an immunosuppressive regimen of mycophenolate mofetil, tacrolimus and prednisolone. She was in respiratory distress and her progressively worsening general condition prompted admission to the intensive care unit (ICU). With a diagnosis of pneumonia due to the presence of pneumonic infiltration on chest x-ray, empirical treatment was initiated with a combination of cefoperazone-sulbactam, clarithromycin and oseltamivir, which was continued for 14 days. She was later transferred to the ward.

Despite undergoing renal transplantation a year before, she developed chronic renal failure while under follow-up in the ICU and was put on a hemodialysis program for the purpose of which vascular access was achieved *via* an arteriovenous fistula on her left arm. However, subsequent infection at the site of the fistula was treated with cefepime at a renal dose (500 mg *i.v.* every 24 hours). On the third day of antibiotic treatment, a sudden change in the patient's state of consciousness was observed, with marked lethargy and non-responsiveness to vocal stimuli. Neurological examination showed no focal deficits. The blood pressure was within the normal range. Magnetic resonance imaging of the brain was normal. Cerebrospinal fluid examination was negative, and liver function was normal. She was again transferred to the ICU with continuous EEG monitoring (Figure 2), the findings of which indicated the diagnosis of cefepime-re-

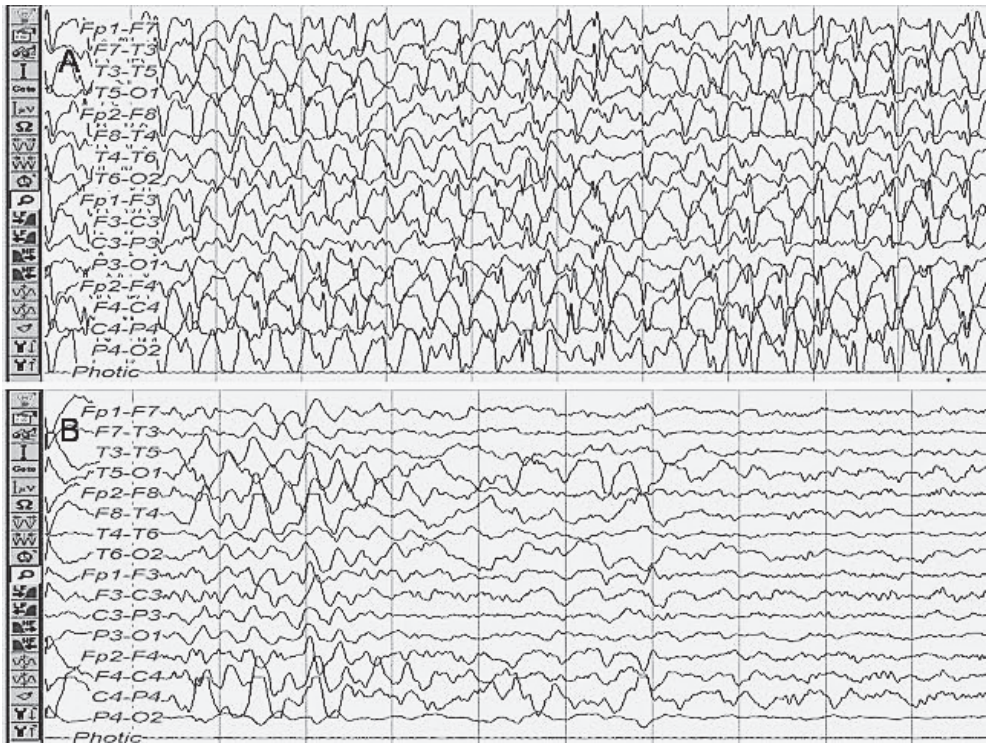

FIGURE 2. Case 2 electroencephalogram (EEG): continuous generalized spike, spike wave and slow wave discharges (A); interictal EEG pattern after diazepam administration (B) (amplitude 200 μv, low filter 1 Hz, high filter 35 Hz).

lated encephalopathy. Cefepime was discontinued with no discernible improvement in her condition after 24 hours. EEG findings, which were re-evaluated by a pediatric neurologist, were deemed more consistent with the diagnosis of NCSE. Following a bolus of diazepam, dramatic improvement was observed. She did not suffer another seizure and antiepileptic treatment was not deemed necessary.

DISCUSSION

Cefepime-induced neurotoxicity generally manifests itself as encephalopathy, myoclonic jerks, epileptic seizures and coma (1). As in our second patient, it may also result in NCSE. Convulsions and NCSE are by far the most common neurologic side effects (2). However, to the best of our knowledge, our case report is the first to describe convulsive SE in a patient with normal renal function.

Predisposing factors for cefepime-induced neurotoxicity include high drug dose (>4 g/day), decreased renal clearance of the drug, increased levels of unbound antibiotic (in renal failure), increased cerebral penetration (as in meningitis), and age >50 (7). Our second patient had at least one of these predisposing factors.

Intraventricular injection of β-lactams has been shown to precipitate seizures in animal studies (8). Cephalosporins, which structurally resemble bicuculline, a γ-aminobutyric acid (GABA) inhibitor, increase the levels of the excitatory amino acid glutamate in terminal nerve ends, while also reducing GABA levels. Despite these effects, cephalosporins have only been shown to result in convulsions if given in high doses or in the presence of uremia or meningitis, conditions that disrupt the blood-brain barrier (9). Even then, NCSE rather than convulsive SE would be expected (9).

Although several cases of NCSE may be encountered in the literature to date, convulsive SE has not been reported in association with cefepime (2, 4-6). Our first patient had uncontrolled epilepsy, which prompted initiation of ketogenic diet. Following a 30-day seizure-free period, he unexpectedly developed convulsive SE after 2 doses of cefepime, despite having normal renal function. Previous studies have shown that patients on ketogenic diet may develop a seizure 90 minutes after a 50-min infusion of glucose (10). The findings of this study suggest that any condition that increases blood glucose levels in a patient on ketogenic diet may result in a seizure.

Cefepime has been reported to increase blood sugar (11), and we believe that with this mechanism our patient developed convulsive SE, rather than *via* its effect on GABA. The high blood glucose level following initiation of cefepime treatment in our patient supported this scenario. Additionally, previous studies have shown the cefepime GABA-associated neurotoxicity generally developed after 3-5 days of

treatment (2), whereas our first patient developed neurotoxicity on the first day of treatment. This may support our hyperglycemia theory. We recommend that cefepime should be used with caution in patients with drug-resistant epilepsy on ketogenic diet. On the other hand, our second patient also responded well to benzodiazepines, which exert their effect *via* GABA-receptor related mechanisms, in support of the GABA theory.

Cefepime-induced encephalopathy has a distinctive pattern on EEG, characterized by continuous bilateral and rhythmic triphasic sharp wave activity, with a high voltage positive phase that is preceded and also followed by a lower amplitude negative wave (1). NCSE is an epileptic condition lasting for >30 minutes, clinically manifested by an altered mental state and associated with continuous epileptiform activity on EEG (3). The clinical presentations of NCSE and encephalopathy are very similar, and distinguishing their EEG findings may also be very challenging (12-14). Nevertheless, the detection of triphasic waves with a frequency greater than 1 Hz and a spiky morphology are more suggestive of NCSE as a possible diagnosis (2). At the same time, a rapid response to diazepam also supports the diagnosis of NCSE.

Our aim in sharing our experience through these two cases of cefepime-related SE is to underline the importance of prescribing cefepime with caution in patients with renal failure or uncontrolled epilepsy, and avoiding it completely in patients on ketogenic diet.

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SAŽETAK

Status Epilepticus povezan s cefepimom

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Cefepim je cefalosporinski β-laktamski antibiotik četvrte generacije. Neurotoksični učinci cefepima su nejasan govor, drhtavica, encefalopatija i konvulzije. Prikazujemo dva slučaja 7-godišnjeg dječaka i 16-godišnje djevojke kod kojih je nastupila neurotoksičnost povezana s cefepimom. Prvi bolesnik je imao nekontroliranu epilepsiju i bio je stabilan mjesec dana dok je bio na ketogenoj dijeti, a onda je nastupio konvulzivni status epilepticus nakon dvije doze cefepima koji je primio zbog celulitisa. Druga bolesnica je bila tipičan slučaj s cefepimom povezane neurotoksičnosti zbog zatajenja bubrega. Prema našim saznanjima, dosad nije opisan konvulzivni status epilepticus udružen s terapijom cefepimom, što upućuje na važnost ovih prvih slučajeva.

Ključne riječi: cefepim; status epilepticus; neurotoksični sindromi; ketogena dijeta; konvulzije