Cefepime-induced Encephalopathy with Triphasic Waves in Three Asian Patients

Dear Editor,

Cefasporins such as cefepime are beta-lactam antibiotics with a broad antimicrobial spectrum. They are commonly used as first-line agents in the treatment of many infections.[1] Reversible encephalopathy is a known neurotoxic complication of cefalosporins.[2] Previous case reports have documented triphasic waves on electroencephalography (EEG) in cephalosporin-induced encephalopathy.[1-4] Cefalosporin-induced encephalopathy with triphasic waves has not been previously reported among Asians. We report 3 Asian patients with toxic encephalopathy and documented triphasic waves on EEG while on treatment with cefepime.

Patient 1

A 77-year-old Chinese man with end-stage renal failure on haemodialysis presented with acute pancreatitis. He was started on intravenous ceftriaxone for 6 days before the antibiotic cover was changed to intravenous cefepime at 2 g twice a day. After 4 days of cefepime, he became confused and developed myoclonus. The initial EEG (Fig. 1a) showed semi-periodic, generalised but predominantly bifronto-central triphasic waves at 1 to 2 Hz.

There was mild abnormality of liver function tests: bilirubin 9 umol/L, alkaline phosphatase (ALP) 319 U/L, alanine aminotransferase (ALT) 76 U/L, and aspartate aminotransferase (AST) 38 U/L. The ammonia level was normal (17 umol/L). His renal function did not deteriorate: the baseline serum urea was 8.4 mmol/L and creatinine 371 mmol/L while serum urea was 7.8 mmol/L and creatinine 276 mmol/L when he was encephalopathic. He continued to receive regular haemodialysis when he was encephalopathic. Three days after the cessation of cefepime, he was less confused. The repeat EEG (Fig. 1b) was normal.

Patient 2

A 71-year-old Indian man with alcohol-related liver cirrhosis was admitted for otitis media. He was started on intravenous ceftriaxone and ciprofloxacin for 2 weeks before being given intravenous cefepime at 2 g twice a day instead. After 3 days of cefepime, he became confused and developed asterixis. The initial EEG showed periodic generalised triphasic waves at 1 to 2 Hz, localised maximally over the fronto-central regions.

His liver function did not deteriorate: baseline serum bilirubin was 11 umol/L, similar to the level of 10 umol/L while encephalopathic. The ammonia level (22 umol/L) and renal function (serum urea 4.4 mmol/L, creatinine 129 mmol/L) were normal. Two days after cefepime cessation, the confusion and asterixis resolved. A repeat EEG showed intermittent generalised slow waves with disappearance of triphasic waves.

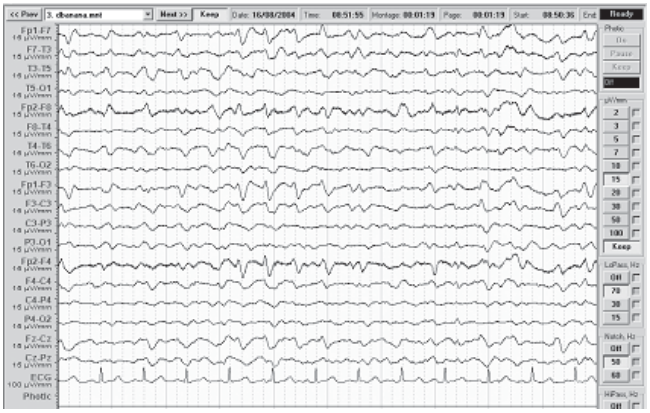

Fig. 1a. Bipolar montage EEG for patient 1 when he was encephalopathic showing triphasic waves.

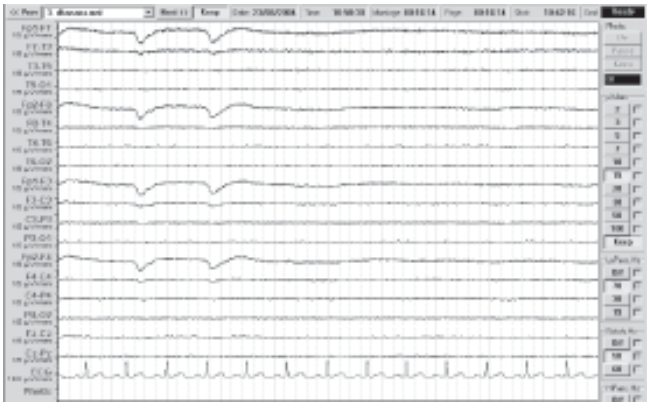

Fig. 1b. Bipolar montage EEG for patient 1 after the encephalopathy resolved with cessation of cefepime showing resolution of triphasic waves.

Patient 3

A 59-year-old Chinese lady with end-stage renal failure on haemodialysis presented with infected gangrene of the right big toe. She was started on intravenous vancomycin and had a right big toe disarticulation. Due to ascending cellulitis, a right below-knee amputation was subsequently performed. After 2 weeks of intravenous vancomycin, the antibiotic was changed to intravenous cefepime 1 g once a day, taking into account dosing adjustment for her renal function. After 2 days of cefepime, she became drowsy and confused with myoclonic jerks of both upper limbs. The initial EEG showed periodic triphasic waves at around 0.5 Hz, localised maximally over the fronto-central regions.

Liver function tests were normal: bilirubin 7 umol/L, ALP 98 U/L, ALT 15 U/L, and AST 19 U/L. Her renal function did not deteriorate and she was continued on regular haemodialysis. The baseline serum urea was 25.5 mmol/L and creatinine 662 mmol/L, while urea was 19.1 mmol/L and creatinine 602 mmol/L when she was encephalopathic. Four days after cessation of cefepime, she was alert and orientated. Her myoclonus resolved. A repeat EEG 7 days after cessation of cefepime showed intermittent generalised slowing with no triphasic wave.

Conclusions

Metabolic and toxic encephalopathy, especially uraemic and hepatic, are frequently associated with triphasic waves on EEG.[5] Neurotoxicity is a known adverse effect of cefalosporins including cefepime[1-4] and can be manifested by encephalopathy, myoclonus and asterixis as demonstrated in our patients. The exact mechanism for the neurotoxicity is not certain with postulated mechanisms including induction of endotoxins and thus liberation of cytokines as well as decreasing brain inhibition mediated gamma aminobutyric acid.[6] Literature review revealed few published cases of cefalosporin causing encephalopathy with triphasic waves, most with renal impairment. There is a recent report of cephalosporin-induced encephalopathy in a patient with normal renal function.[6] None of these patients were of Asian origin. Cefepime is a fourth-generation cephalosporin with a wide spectrum of activity. There have been previous reports of encephalopathy with triphasic waves associated with the use of cefepime.[3,4,6]

The confusion in all 3 patients might have been a result of septic encephalopathy, though triphasic waves not typical of septic encephalopathy. None of these patients had worsening of pre-existing renal or hepatic function which thus was not likely the cause of the encephalopathy with triphasic waves. The temporal relation to the starting of cefepime and appearance of encephalopathy with triphasic waves and disappearance of these after stopping cefepime pointed to the diagnosis of cefepime-induced toxic encephalopathy.

In patient 1, the dose of cefepime was not titrated according to renal function, likely precipitating neuro-toxicity. As cefepime is metabolised in the liver, the underlying liver impairment in patient 2 might have contributed to the development of toxic encephalopathy. Patient 3 developed encephalopathy with triphasic waves, even though the cefepime dose was adjusted according to her renal function. It appears that pre-existing renal or liver impairment lowers the threshold for cefepime-induced encephalopathy with triphasic waves. Cefepime is mainly excreted via renal elimination.[7] Haemodialysis removes a large portion of cefepime from the body, approximately 40% to 60% over 3 hours of haemodialysis.[7] Thus, the dose of cefepime should be adjusted in renal impairment and timed appropriately in patients on haemodialysis.[7]

These are the first case reports of Asians with cefepime-induced encephalopathy with triphasic waves. Cefalosporins should be considered a potential cause of toxic encephalopathy associated with triphasic waves when there is a temporal relationship with its use, particularly when there is no deterioration in renal and hepatic function. As shown in these 3 cases, recognition of cefalosporin-induced encephalopathy and appropriate management, with cessation of cefalosporin use can result in a reversal of the encephalopathy.

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