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Journal of the Chinese Medical Association 74 (2011) 87–90
www.jcma-online.com

Case Report

Cefepime-related encephalopathy in peritoneal dialysis patients

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Received May 19, 2010; accepted August 21, 2010

Abstract

Encephalopathy or neurotoxicity can occur with cefepime use in patients with impaired or relatively normal renal function. However, few articles have examined the relationship between cefepime's adverse effects and peritoneal dialysis.

Here, we report the case of an 80-year-old woman with chronic renal failure on peritoneal dialysis that developed agitation, confusion, and dystonia after cefepime administration for 2 days. The clinical and electroencephalographic abnormalities improved after discontinuation the drug. We review the role of peritoneal dialysis in the development of cefepime-induced encephalopathy. Peritoneal dialysis is a less efficient way to eliminate cefepime than hemodialysis. Short-term hemodialysis might be considered to facilitate elimination of the drug in patients who have developed neurotoxicity.

Keywords: Cefepime; Electroencephalogram; Encephalopathy; Peritoneal dialysis

1. Introduction

Cefepime is a fourth-generation cephalosporin used to treat severe infection, which is mainly excreted unchanged by kidney.[1,2] There were several series of cases with cefepime-associated reversible encephalopathy or nonconvulsive-status epilepticus in patients with variable level of impaired[3–9] or relatively normal[10,11] renal function. The incidence has been reported to be 1%. Among renal-impaired patients, the incidence rose to 4.5–16.6%.[12] Up to now, there have been only four reported cases of cefepime-associated neurotoxicity in uremic patient using continuous ambulatory peritoneal dialysis (CAPD) as renal replacement therapy. Also, there was no literature focusing on the role of peritoneal dialysis in the development of such adverse events.

Here, we present a case with chronic renal failure under CAPD, who developed incompletely reversible encephalopathy after 2-day administration of cefepime.

2. Case report

An 80-year-old woman presented with a 3-month progressive decline of mental status and daily living abilities. She had a medical history including hypertension, coronary artery disease, mild cognitive impairment, and chronic renal failure under CAPD. On presentation, she could stand with assistance, but could not walk. She had a score of 8 on the Mini-Mental State Examination.

A brain magnetic resonance imaging (MRI) showed profound leukoaraiosis. The patient was afebrile during the hospital stay. However, initial blood tests showed leukocytosis along with elevated C-reactive protein (CRP) level. Pneumonia was initially suspected, and cefmetazole 2 g/day was empirically used for 2 weeks. Abdominal computed tomography demonstrated fluid accumulation in the uterus. A diagnostic dilation and curettage confirmed the existence of endometritis. We substituted the antibiotic regimen with

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1726-4901/$ - see front matter
doi:10.1016/j.jcma.2011.01.017

cefepime 2 g/day and metronidazole 1 g/day (Day 1). The patient's cognitive function improved, and she could respond functionally with single words. However, the patient developed acute delirium and refused oral intake, had no verbal output and showed agitation on Day 2. On Day 3, she had head-turning to the right with a dystonic posture. A follow-up blood test showed improved white cell counts and CRP level, but her mental status kept on worsening. All the serologic metabolic analyses were normal. Antibiotic-related encephalopathy was suspected and we shifted cefepime and metronidazole to piperacillin/tazobactam 4.5 g/day immediately. Electroencephalogram (EEG) showed periodic short-interval diffuse discharges with shifting predominance on Day 4 (Fig. 1A). The consciousness level improved gradually thereafter. The patient was responsive to verbal stimuli on Day 6 and able to obey orders intermittently on Day 7. An EEG on

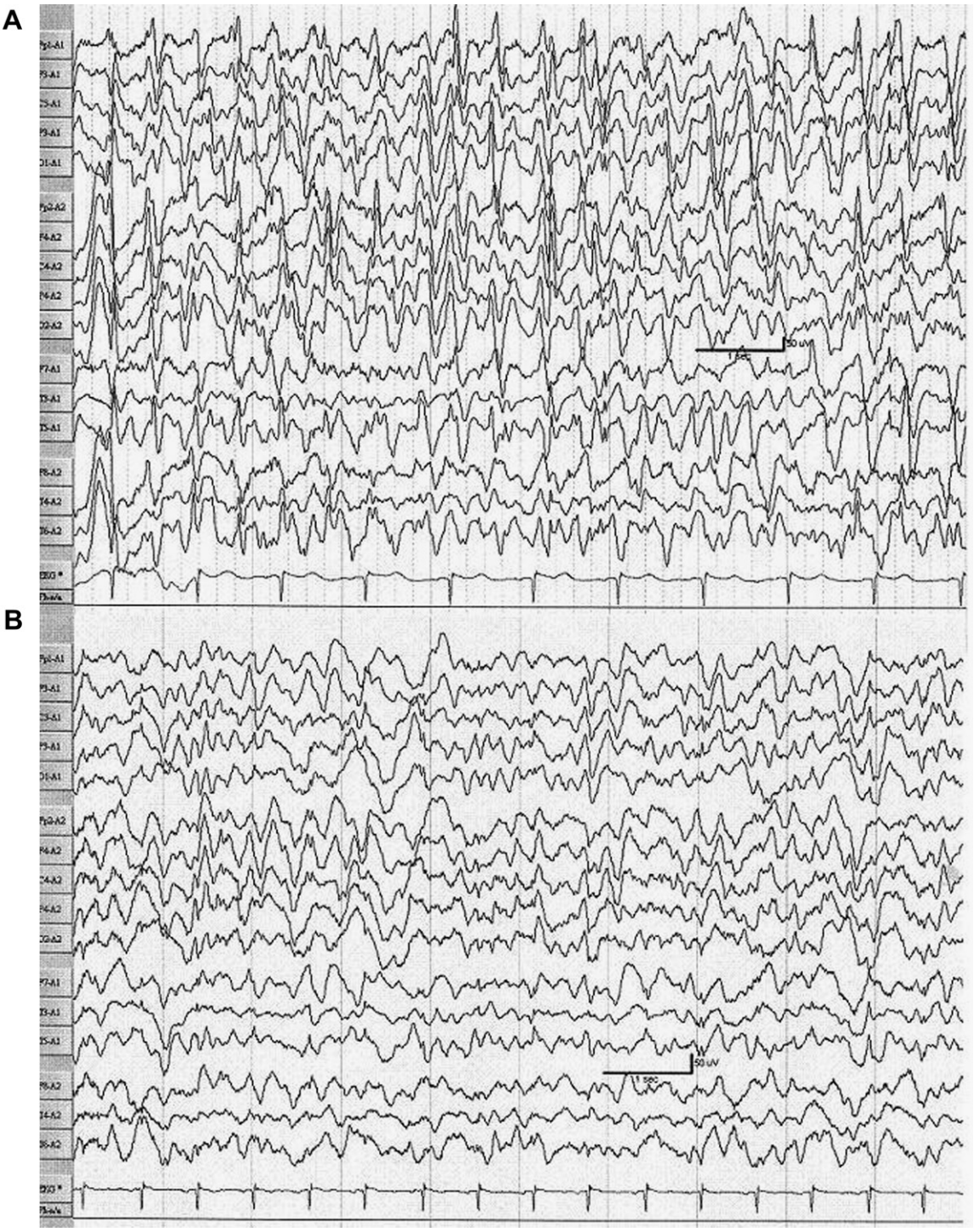

Fig. 1. (A) Three days after cefepime therapy, EEG showed periodic short-interval diffuse discharges with shifting predominance, along with diffuse background slow waves with 4–6 Hz; (B) Two weeks after cefepime injection, EEG showed partial recovery.

Table 1
Clinical features of five peritoneal dialysis patients with cefepime-induced neurotoxicity

References (year)	Age/sex (yr)	Creatinine level (mg/dL)	Cefepime dosage	Clinical manifestation	Latency (d)	Treatment	Outcome
Chow et al. (2001)[6]	69/F	14.2	2 g/d	Confusion	6	AED	Resolved
Chow et al. (2003)[7]	59/M	14.1	5 g/d	Confusion, obsessive ideas, dysmetria	2	NR	Resolved
	60/F	9.5	1 g/d	Disorientation, irrelevant speech	9	NR	Resolved
Alpay et al. (2004)[9]	15/M	NR	12.5 mg/kg/d	Ataxia, asterixis, confusion	6	BZD, AED	Resolved
Lin (current study)	80/F	5.6	2 g/d	Confusion	2	Stop cefepime	Improved

AED = antiepileptic drugs; BZD = benzodiazepine; F = female; M = male; NR = not reported.

Day 14 showed diffuse background slow wave without epileptiform discharges (Fig. 1B). At a 2-month follow-up evaluation, she still had not improved to the baseline level.

3. Review of literature

A literature review was performed by using PubMed with keywords including cefepime, encephalopathy, neurotoxicity, and peritoneal dialysis (1999–2008). There were three case reports found, including four patients (two males and two females). We collected information about the patients' age of onset, serum creatinine level, daily cefepime dosage, and latency from initiation of treatment to onset of neurological toxicities.

4. Results

In addition to our patient, there were only four patients receiving peritoneal dialysis (two males and two females) who suffered from cefepime-induced neurotoxicity reported in the literature (Table 1), including three adults who developed reversible encephalopathy[6,7] and one 15-year-old adolescent who suffered from nonconvulsive-status epilepticus.[9] Including our patient, the median age was 60 years. The median latency was 6 days. For the four adult cases, the accumulative dose was 4–12 g. Our patient had the oldest age, the shortest latency from initiation of treatment to symptoms onset among the five cases and the lowest accumulated dose among the four adults.

5. Discussion

Because of the temporal association of the symptom onset and drug administration, as well as symptom improvement after drug discontinuation, we diagnosed the patient as having antibiotic-related encephalopathy. Infection related–consciousness disturbance was not likely because the symptoms developed along with improvement of white blood cell counts and CRP level. Uremic encephalopathy was excluded because of the stable renal function test data.

Besides cefepime, this patient was also administered with metronidazole at the same time. However, the clinical presentations of our patient were not compatible with previously reported metronidazole-associated neurotoxicities, which encompassed encephalopathy, cerebellopathy, and dentate nuclei involvement demonstrated *via* MRI and tended to occur after prolonged use.[13] Although no affirmable causality could be claimed, we indicated that cefepime was likely the cause of the clinical and electroencephalographic manifestations of the present case.

All previous cases of cefepime-related encephalopathy and neurotoxicity, with the exception of two cases, had renal insufficiency or failure.[10,11] Except for renal function impairment,[12] no other independent risk factors have been reported. The mechanisms involved in the development of such neurotoxicity have not been clearly understood. Decreased γ-aminobutyric acid releasing from nerve terminals and subsequent increased excitatory neurotransmission,[14–16] γ-aminobutyric acid transporter system dysfunction,[17] and induction of endotoxins along with the release of tumor necrosis factor-alfa[18] have been proposed to explain the pathophysiology.

CAPD is less efficient at clearing cefepime than hemodialysis. Dialytic clearance of cefepime by peritoneal dialysis is only 9% of that reported for the hemodialysis.[19] The half-life of cefepime is approximately 2.2 hours in adults with normal renal function[1,20] but prolonged to 18 hours in CAPD patients.[19] A dosing interval of 70.7 hours had been calculated for patients with CAPD.[19] A dosing interval of 24 hours, such as used in the present case, may cause accumulation of the drug in plasma, peritoneal fluid, and even cerebrospinal fluid, which in turn induces neurotoxicity. The lower clearance of cefepime in CAPD patients may explain the slow and partial recovery. For such high-risk patients, the dosage of renal excreted antibiotics including cefepime should be adjusted cautiously. There were less reported cases of penicillin-induced encephalopathy than those due to cephalosporin. Piperacillin/tazobactam may be an alternative agent when broad-spectrum antibiotics are clinically necessary.

There have been some articles indicating the beneficial role of short-term hemodialysis in treating patients suffering from the neurotoxicity associated with cefepime.[2,5] Thus, short-term hemodialysis may provide better and more rapid improvement of clinical status in our patient.

Reviewing all the published articles, preexisting cognitive impairment had not been taken into account. Cefepime dose as low as 9 g previously caused neurotoxicity in patients with CAPD. However, our patient developed symptoms after receiving only 4 g of cefepime. Our patient had underlying cognitive impairment and leukoaraiosis as demonstrated by brain MRI, which may have further contributed to the vulnerability and poor reversibility of this episode. However, a longer follow-up may be needed to clarify reversibility.

Acknowledgment

This study was supported in part by grants from the Taipei Veterans General Hospital (V99C1-047).

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