Neurotoxicity Secondary to Intraperitoneally Administered Cefepime: Report of Two Cases

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Cefepime is a broad-spectrum antibiotic used successfully as empirical monotherapy in patients with continuous ambulatory peritoneal dialysis (CAPD) peritonitis. Unfortunately, current intraperitoneal dosage recommendations are based on clinical experience rather than solid pharmacokinetic knowledge. We report two cases of cefepime-related confusion in CAPD peritonitis treated with intraperitoneal cefepime at a commonly used dosage. High peritoneal membrane transport characteristics and deteriorating residual renal function may alert clinicians to the risk of cefepime-induced neurotoxicity. Pharmacokinetic data are essential for rational prescription when the drug is to be administered intraperitoneally. [Hong Kong J Nephrol 2004;6(2):106–8]

Key words: cefepime, cephalosporins, intraperitoneal, continuous ambulatory peritoneal dialysis, peritonitis

INTRODUCTION

Cefepime is a fourth-generation cephalosporin with broader spectrum antimicrobial activity than most third-generation cephalosporins. In addition to retaining good activity against Gram-positive organisms, cefepime demonstrates expanded Gram-negative coverage when compared with other widely used cephalosporins such as ceftazidime [1]. Its versatility makes it an ideal choice as empirical monotherapy for the treatment of continuous ambulatory peritoneal dialysis (CAPD) peritonitis while waiting for bacterial culture results [2].

Despite the lack of pharmacokinetic data, cefepime has been successfully administered intraperitoneally to treat CAPD peritonitis [2,3]. Our center has developed a similar protocol for the empirical treatment of CAPD peritonitis in patients who are non-anuric. The standard regimen involves a loading dose of 1 g followed by a maintenance dose of 250 mg four times per day, all delivered intraperitoneally during each 2 L dwell. We report two cases of neurotoxicity related to the use of cefepime in this regimen.

CASE REPORTS

Case 1

A 44-year-old housewife with diabetic nephropathy on CAPD since August 2002 suffered from her first episode of CAPD peritonitis in November 2002. She was given cefepime for 4 days according to our standard regimen, before switching to oral levofloxacin according to bacterial sensitivity (dialysate grew *Acinetobacter* sp). She was cured with no side effects.

In February 2003, annual assessment showed a residual creatinine clearance of 1.39 mL/min/1.73 m².
A peritoneal equilibration test (PET) classified her as a “high average” transporter (dialysate to plasma creatinine ratio at 4 hours, 0.81).

In May 2003, she was admitted again for CAPD peritonitis and was started on cefepime empirically according to our standard regimen. Cefepime was changed to intraperitoneal cefuroxime 2 days later, according to the culture sensitivity result (dialysate grew Enterobacter sp). The treatment was successful, without any complications.

She was admitted in October 2003 for abdominal pain and cloudy dialysate. The dialysate white cell count was 3,280/mm³ with 88% polymorphs. She was treated for CAPD peritonitis and empirically started on our standard regimen of intraperitoneal cefepime. The dialysate cleared up after 4 days of treatment.

On day 5, she became dull and showed subtle dysarthria. She was arousable with full orientation to time, place, and person. She was afebrile and her neck was supple. There was generalized weakness and hyporeflexia. Plantar jerks were downward. There were no other demonstrable neurologic signs. Plasma urea concentration was 23.6 mmol/L and creatinine concentration was 1,117 μmol/L. Electrolytes, including calcium, were normal. Plain computed tomography (CT) brain scan was normal.

Her condition deteriorated over the next 2 days. On day 7, she had become confused, disoriented, and obtunded. She required physical restraint and insertion of a nasogastric tube for feeding. The dialysate grew Klebsiella and Enterobacter species, both sensitive to cefepime. Cefepime-related neurotoxicity was suspected and the dosage of intraperitoneal cefepime was halved to 125 mg four times per day.

Her condition improved markedly over the next 2 days. On day 9, she was fully orientated with no residual neurologic deficit. The nasogastric tube was removed.

The prompt clinical response and dialysate culture sensitivity results prompted us to continue cefepime monotherapy at the reduced dose. This episode of peritonitis was cured without relapse after a 2-week course of cefepime. Subsequently, her residual renal creatinine clearance was reduced to 0.02 mL/min/1.73 m².

**Case 2**

A 65-year-old housewife with diabetic nephropathy was started on CAPD in February 2002. PET in June 2002 classified her as a “high” transporter (dialysate to plasma creatinine ratio at 4 hours, 0.87). Residual renal creatinine clearance was 2.31 mL/min/1.73 m² in October 2003.

She was admitted in March 2004 for her first episode of CAPD peritonitis. She was treated with intraperitoneal cefepime according to our standard regimen. Her dialysate started to clear up from day 2.

She became less talkative on day 3, despite being fully conscious and able to give her name. There were no focal neurologic signs. Plasma urea concentration was 24.2 mmol/L and creatinine concentration was 853 μmol/L. Electrolytes and thyroid function test were normal. Urgent CT brain scan showed a tiny hypodensity over the right corona radiata, which was considered irrelevant to the whole clinical picture.

On day 4, she became totally confused, requiring restraint and nasogastric tube feeding. She demonstrated only occasional, incomprehensible speech. Lumbar puncture yielded a sterile specimen with normal biochemistry and no white blood cells. Cefepime-related confusion was suspected and therapy was changed to intraperitoneal cefazolin. The dialysate later grew coagulase-negative Staphylococcus sensitive to penicillin and cloxacillin.

Her confusion gradually resolved over the next 3 days. By day 7, she had become fully orientated, although she still complained of malaise. On day 9, she was able to walk with a frame. After an extra week of rehabilitation, she was able to walk unaided, with no residual neurologic deficit. Her CAPD peritonitis was cured with a course of intraperitoneal cefazolin.

**DISCUSSION**

The conventional management of CAPD peritonitis has been intraperitoneal administration of antibiotics, and treatment protocols are often derived from clinical experience rather than pharmacokinetic or pharmacologic data [4]. The pharmacokinetics of intravenous cefepime have been studied in patients with severe renal insufficiency [5] and those undergoing CAPD [6]. In contrast, the pharmacokinetics of intraperitoneal cefepime have not been so well described.

In the treatment of CAPD peritonitis, the importance of bactericidal plasma versus intraperitoneal concentrations of antibiotic is uncertain [4]. In general, a drug moves rapidly from the peritoneal space to the systemic circulation, in contrast to the slow appearance of the same drug in the peritoneal dialysate when administered by the intravenous route. This is termed unidirectional drug transport [7]. It can be inferred that intraperitoneal administration of cefepime leads to initial peritoneal fluid drug levels that cannot be achieved by an equivalent dose administered intravenously. Dialysate effluent drug measurement is thus particularly important in any pharmacokinetic study of patients on CAPD. In a single case report, intraperitoneally administered cefepime led to sustained therapeutic plasma levels. However, the dialysate effluent drug level was not measured [8].

Nevertheless, intraperitoneal cefepime, administered at a loading dose of 2 g followed by a daily main-
Cefepime, a fourth-generation cephalosporin, has been used as an effective empiric antimicrobial agent for CAPD peritonitis [2,3]. In our center, a similar regimen has been used very successfully over the past 2 years.

Despite a good safety profile, adverse central nervous system reactions due to cefepime have probably been underreported [9]. Possible side effects include confusion with temporospatial disorientation, myoclonus, and seizures. Both advanced age and renal insufficiency are common risk factors for neurotoxicity [9–11]. Apart from a case of CAPD peritonitis treated accidentally with a high daily dose of 4 g [9], intraperitoneal cefepime has been reported to be safe and well tolerated [2]. To our knowledge, this is the first report of neurotoxicity developing in patients treated with 1 g intraperitoneal cefepime daily.

Our first case had been given intraperitoneal cefepime twice previously without any neurologic toxic effect. We speculate that the better-preserved residual renal function, coupled with a lower cumulative dose, might be the underlying reason.

The diagnosis of cefepime-related neurotoxicity may be questioned without measuring serum and cerebrospinal fluid (CSF) drug levels (assay not available in Hong Kong). However, a presumptive clinical diagnosis can often be made in a susceptible patient with a typical clinical picture and complete recovery on withdrawal of the drug [12,13]. Although electroencephalographic (EEG) abnormalities have been described [9–11], the findings are far from universal or diagnostic. Unfortunately, EEG services were not available to our patients and we had to rely heavily on our clinical judgment. Of note, cefepime was continued in the first case, albeit at a lowered dose. Based on the Naranjo adverse drug reaction probability scale [14], both of our cases were classified as “possible adverse drug reactions”.

Our patients might be particularly susceptible to the toxicity of intraperitoneally-administered cefepime. Case 1 was a high-average transporter while Case 2 was a high transporter. It is possible that they attained higher serum bioavailability compared with low transporters. Increased membrane permeability during peritonitis [7], impaired active transport of cephalosporins from CSF to blood [9,10], decreased protein binding in uremia, and decreased drug clearance in uremia [12] all predispose these patients to neurotoxicity.

From July 2002 to June 2004, we treated more than 70 episodes of CAPD peritonitis with our empirical regimen of intraperitoneal cefepime. Cefepime-related neurotoxicity is, thus, uncommon but should be borne in mind, particularly in patients who are anuric. Theoretically, the pharmacokinetic data of parenteral cefepime are totally irrelevant when the drug is administered intraperitoneally. Pharmacokinetic studies on intraperitoneally-administered cefepime in patients with CAPD peritonitis are essential in guiding rational prescription at correct dosages.

REFERENCES