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Case Report

CASE REPORT

Cefepime-induced encephalopathy with normal renal function

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Abstract

Cefepime is a fourth-generation cephalosporin that is frequently used in a wide array of infections. Since approval for use, concerns have been raised due to adverse effects including seizures, encephalopathy and myoclonus especially if renal dysfunction is present. Despite having appropriate renal dose adjustments, cases have been found with adverse neurological effects. On this occasion, we present a case of a patient with normal renal function that had demonstrated cefepime-induced encephalopathy with full resolution of symptoms following discontinuation of the medication.

INTRODUCTION

Cefepime is a fourth-generation cephalosporin with antibacterial spectrum covering aerobic gram-positive and gram-negative bacteria including *Pseudomonas aeruginosa* [1]. Cefepime has been recommended for a wide array of infections such as hospital-acquired pneumonia, febrile neutropenia, skin/soft tissue infections and intra-abdominal infections [1, 2]. Similar to other cephalosporins, cefepime is largely excreted via the kidneys with 85% unchanged in the urine, and the remainder is metabolized by the body to N-methylpyrrolidine and a 7-epimer isomer [3]. In 2002, the Food and Drug Administration (FDA) adjusted the labeling to account for increased risk of seizures, encephalopathy and myoclonus, especially in the setting of renal impairment [2]. These adverse events were mostly seen in patients who were at the age of 50 years or greater and had renal dysfunction and typically without dose adjustments [4]. Here, we present a case of encephalopathy in the setting of normal renal function undergoing treatment with cefepime.

CASE REPORT

Our patient is a 76-year-old African-American female who presented to the hospital with generalized weakness and a past medical history of adrenal insufficiency, noninsulin-dependent diabetes mellitus, hypertension and hyperlipidemia. The patient endorsed cough with sputum production without fever and chills. The patient had a recent hospitalization for hyponatremia secondary to adrenal insufficiency. The pulse was 108 beats/min with the remainder of the vital signs within normal limits. Pertinent positives on exam included pulmonary findings of bibasilar crackles and decreased breath sounds. Lab tests performed showed the following: sodium 121 mmol/l (135–145 mmol/l), potassium 5.2 mmol/l (3.5–5.0 mmol/l), blood urea nitrogen 11 mg/dl (8–20 mg/dl) and creatinine 0.58 mg/dl (0.40–1.30 mg/dl). A white blood cell count was 11.1 mg/dl (4.0–11.0 mg/dl) and hemoglobin at a baseline of 10.6 mg/dl (11.5–16.0 mg/dl).

Chest X-ray displayed moderate to large bilateral pleural effusions with associated atelectasis and minimal patchy infiltrate at the right base. The patient was given intravenous fluids (normal saline), vancomycin and cefepime 2 g every 8 h for positive SIRS criteria with a presumed pulmonary source. The sodium level improved to 127 mmol/l on the following day and remained near low 130–135 mmol/l ranges for the remainder of the hospitalization. Initial blood cultures grew two out of four bottles with coagulase negative *Staphylococcus*.

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Clinically, the patient was improving until Hospital Day 5, where she was found lethargic and not conversational. The patient was unable to perform basic commands. Vitals at that time were within normal limits with no febrile episodes. Labs were within normal limits, except with sodium at 133 mmol/l. A head computed tomography without contrast had no acute intracranial abnormalities with no change in moderate chronic white matter ischemia. A repeat chest X-ray demonstrated no new consolidation with moderate basilar effusions and atelectasis. Repeat blood and urine cultures showed no growth. Urinalysis had moderate blood and protein 100 mg/dl with negative nitrites and leukocytes. A lumbar puncture performed showed clear fluid with normal pressure. Central spinal fluid results included: glucose 82 mg/dl (45–75 mg/dl), protein 40 (15–45 mg/dl), WBC 1 mm^3 and RBC 4 mm^3. A magnetic resonance imaging without contrast showed no acute intracranial abnormality and mild to moderate chronic white matter ischemic changes. An electroencephalography performed demonstrated diffuse slowing with triphasic waves and no electrographic seizures.

The patient was switched to piperacillin–tazobactam, and cefepime was discontinued. A gradual improvement in orientation and response to questioning was seen. The patient was at baseline following 3 days of the discontinuation of cefepime. The patient completed a total of 9-day treatment of antibiotics and was discharged to a subacute nursing facility for further physical therapy. The patient had no further episodes of confusion and lethargy since being discharged.

DISCUSSION

Cefepime was first approved by the FDA in 1997 [3]. This fourth-generation cephalosporin has been used in a wide spectrum of infections for gram-negative and gram-positive infections including *Pseudomonas* coverage [2]. Additionally, this antibiotic has been found to have superior coverage of methicillin-susceptible Staphylococcus aureus (MSSA) [2]. Cefepime is largely excreted via the kidneys with 85% found unchanged in the urine [3]. Adverse effects from treatment were considered rare with most reactions including headaches, nausea and rashes [3].

Following initial approval, cefepime had a label warning added for reports of myoclonus, seizures and encephalopathy with most cases in the setting of renal dysfunction [2]. A study by Jallon *et al.* in 2000 reported 19 cases of severe encephalopathy involving cases of infection being treated with cefepime [5]. The cases included patients aged from 57 to 91 years with renal insufficiency who initially presented with confusion. The electroencephalography displayed diffuse rhythmic triphasic sharp waves. Following discontinuation of cefepime, clinical symptoms resolved showing a likely relation. Another study in 2005 demonstrated three cases with cephalosporin-induced nonconvulsive status epilepticus with renal insufficiency. In each case, the clinical symptoms included altered mental status associated with epileptiform activity with continuous or almost continuous rhythmic generalized bi-triphasic sharp waves on electroencephalography [6].

Cefepime's efficacy and safety were evaluated previously with two meta-analysis studies that measured all-cause mortality [2]. The first study in 2006 evaluated antibiotic treatment for neutropenic fever with 33 trials showing higher all-cause mortality after 30 days with cefepime when compared with other β-lactam antibiotics (RR 1.04, 95% CI 1.24–3.04) [7]. Another study by Yahav *et al.* in 2007 performed another meta-analysis with 57 randomized trials that compared cefepime with other β-lactam alternatives finding a significantly higher all-cause mortality. The study suggested the causes as unrecognized adverse effects such as encephalopathy or involving inadequate antimicrobial efficacy [2, 8]. In 2008, the FDA performed a meta-analysis with 88 clinical trials including the trials from the Yahav *et al.* meta-analysis that concluded no significant difference in mortality observed [2, 9].

Cefepime has been shown to have significant adverse effects even with renal dose adjustments. In 2013, Fugate *et al.* evaluated 100 patients in the intensive care unit setting for neurotoxicity finding 15 patients likely having cefepime encephalopathy and 7 patients considered definite [10]. In this study, four of these patients had the doses of cefepime adjusted for renal function and still experienced adverse effects [10].

Neurotoxicity effects have been considered despite having a normal renal function in previous studies. In 2005, a case with a 79-year-old female with normal renal function who was being treated with cefepime for a pseudomonas urinary tract infection became acutely confused [11]. The patient became acutely confused. The electroencephalography demonstrated continuous generalized sharp and slow wave discharges. The patient was initially treated with lorazepam and valproic acid with limited clinical change. Cefepime was discontinued, and the patient's mental status returned back to baseline gradually over 3 days [11]. Another case report in 2005 demonstrated cefepime and cefixime-induced encephalopathy in a patient with normal renal function with resolution of acute delirium following discontinuation of the cephalosporins on two separate events during the hospitalization [12]. Additionally, a study in 2011 showed epileptiform discharges in 14 of 1120 patients receiving cefepime with most cases having normal renal function [13].

In the present study, the patient had normal renal function and was found to have neurotoxicity secondary to cefepime use. As previously seen, other causes of encephalopathy need to be ruled out such as infectious, metabolic and neurologic etiologies. The electroencephalography had diffuse slowing with triphasic waves similar to previous studies [14]. Despite an extensive workup, no other etiology was discovered with a full recovery back to baseline after 72 h of discontinuation of cefepime. In the setting of acute confusion and use of cefepime, special consideration of alternative antibiotics should be considered if no other etiology has been ascertained even in appropriate renal dose adjustment.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None.

ETHICAL APPROVAL

This study conforms to standards currently applied in the country of origin.

CONSENT

Consent was retrieved for this study.

GUARANTOR

A.M. is the guarantor of this study.

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