Cefepime Induced Encephalopathy in a Non-dialysis Dependent Chronic Kidney Disease Patient: A Case Report

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ABSTRACT

Cefepime is a frequently used fourth-generation cephalosporin antibiotic for a wide variety of infections. Toxic levels of this drug can cause neurological complications. The most common neurological adverse event of cefepime is headache and lightheadedness. Here, we presented a case of cefepime induced encephalopathy in a 57-year-old female patient with acute on chronic kidney disease. With an accurate diagnosis that requires a high index of clinical suspicion, prompt management was instituted. She had full resolution of symptoms following discontinuation of the medication and also emergent dialysis.

Keywords*: Cefepime, encephalopathy, chronic kidney disease.*

INTRODUCTION

Cefepime has a broad antibacterial spectrum covering aerobic for gram-positive and gram-negative bacteria including Pseudomonas.[1] Cefepime was recommended for a wide array of infections such as hospital-acquired pneumonia, febrile neutropenic sepsis as well as soft tissue and intra-abdominal infections.[2]

The neurotoxic effects of Cefepime was first reported in 1999 and the most common being headache and lightheadedness.[3,4] These symptoms are often associated with decreased cefepime clearance in the setting of reduced glomerular filtration rate and increased central nervous system penetration secondary to blood-brain barrier dysfunction.[5] These adverse events are mostly seen in patients who are on renal replacement therapy. It is rarely seen in patients not requiring dialysis. In 2002, the Food and Drug Administration (FDA) adjusted the labelling to account for increased risk of seizures, encephalopathy and myoclonus, especially in the setting of renal impairment.[6]

CASE ILLUSTRATION

A 57-year-old female with stage IIIb chronic kidney disease (CKD) secondary to diabetes mellitus (baseline creatinine of 137 µmol/L), hypertension and dyslipidemia presented with a one-week history of fever, reduced oral intake, nausea lower abdominal pain and acute urinary retention. On examination, she was alert with blood pressure of 138/90 mmHg, pulse rate 98 beats per minute and febrile at 38°C.

Abdominal examination revealed a distended bladder. Therefore emergent catheterization was done. Her blood glucose was 8mmol/L, and urinalysis had leukocyte of 3+. Her renal function test showed raised creatinine level to 246 µmol/L with urea of 11.7 mmol/L, she had no leukocytosis but raised serum C-reactive protein of 5.4mg/dl. She was diagnosed and treated for urinary tract infection and emprically started on intravenous ceftriaxone 2gm once daily.

Ultrasound of urinary tracts showed grossly distended urinary bladder with bilateral hydronephrosis and hydroureter.

On day 3, her urine and blood cultures both grew *Enterobacter species* Beta-Lactamase Group 1, sensitive to cefepime only. Her antibiotic was escalated to intravenous (IV) Cefepime 500mg twice daily. Her renal function was at 267 µmol/L, with an estimated glomerular filtration rate (eGFR) of 16mls/min/1.73m^2. After three days of IV cefepime, she was noted to be disoriented and had incoherent speech. Her conscious level was fluctuating with Glasgow coma scale ranging from 13/15 to 14/15. Capillary plasma glucose was 8mmol/L, other electrolyte parameters and CT brain were all normal. Her neurological manifestations coincide with the initiation of IV Cefepime; thus, the possibility of Cefepime induced encephalopathy (CIE) was entertained.

Electroencephalogram (EEG) showed mild to moderate cerebral disturbance by virtue of excessive theta activity with triphasic waves in keeping with metabolic encephalopathy. The EEG images are as below (**Figure 1**). Therefore, based on clinical manifestations and EEG findings, she was diagnosed with CIE.

Cefepime was withheld, and she underwent two sessions of hemodialysis (HD) lasting 4 hours each which saw a tremendous improvement in her clinical condition with normal orientation and speech. The antibiotic was switched to IV Meropenem for another 5 days after stopping the Cefepime. Her repeated blood and urine cultures were negative and she was allowed to be discharged home. As expected, her renal functions also returned to the baseline (**Figure 2**).

DISCUSSION

Cefepime is a widely used antibiotic in the settings of sepsis and acutely ill. It is a 4th generation cephalosporin with a broad antibacterial spectrum covering aerobic gram-positive and gram-negative bacteria including pseudomonas.[1] It is mainly excreted via the kidneys with 85% unchanged in the urine and the body metabolizes the remainder to N-methylpyrrolidine, a 7- epimer isomer.[1] Approximately 10% of serum cefepime is able to pass through the blood-brain barrier; however in the setting of decreased eGFR, this can increase up to 45%.[5] Treatment with a cephalosporin may also induce endotoxin release which generates cytokines liberation such as tumor necrosis factor- α (TNF- α). TNF-α seems to mediate septic encephalopathy.[7] Alternatively, in an animal study, cephalosporin's may decrease γ-aminobutyric acid (GABA) release from nerve

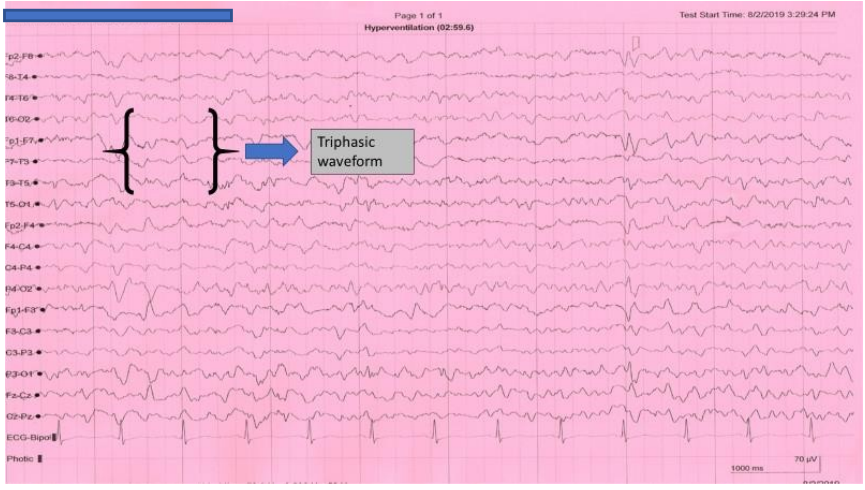

Figure 1. EEG showing encephalopathic disturbances with triphasic waveform.

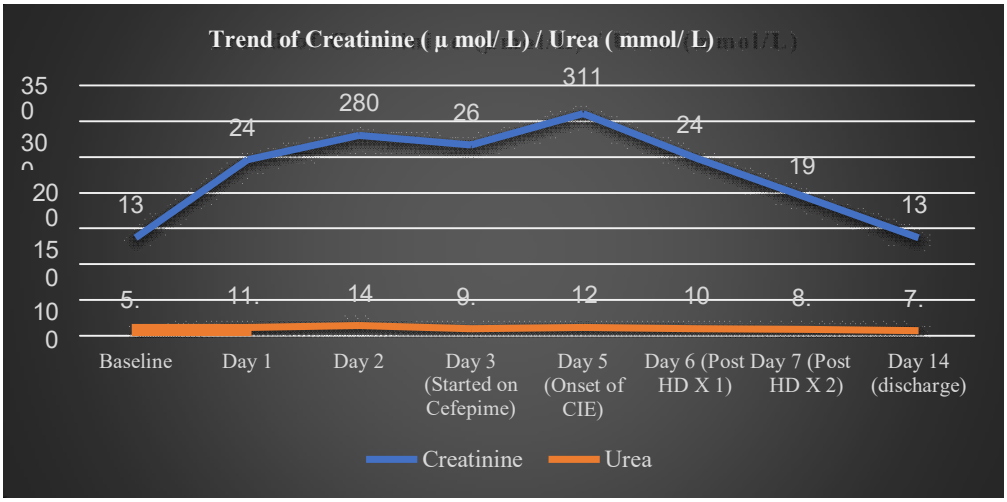

Figure 2. Trend of serum creatinine and urea.

terminals, increase excitatory amino acid release, and exert a competitive antagonism towards GABA.[8] In the settings of acute on chronic kidney disease, the clearance of cefepime is delayed, and in our patient, the blood brain barrier is further compromised due to the underlying bacteremia that can further potentiate risk of encephalopathy.

In patients with end-stage renal disease (ESRD), there are multiple evidence and reports of non-convulsive status-epilepticus and metabolic encephalopathy associated with cefepime.[3] The EEG in these patients shows paroxysmal activity or sharp triphasic waves which are pathognomonic of CIE.[9-11] Cefepime was also found to have significant adverse effects despite renal dose adjustments.[12] Two meta-analysis studies measured all-cause mortality. The first study was in 2006, where it evaluated antibiotic treatment for neutropenic fever with 33 trials showing higher all- cause mortality after 30 days with cefepime when compared to other β-lactams.[13] A second study by Rugate et al. in 2013 evaluated 100 patients from the Intensive Care Unit setting for neurotoxicity and found 15 patients likely to have CIE, and 7 patients were found to be definite. Four patients out of these 7 had their cefepime dose adjusted for their renal function but still experienced adverse effects.[12] The diagnosis of CIE in these studies was made via EEG and also based on clinical features. A case series by the U.S. Food and Drug Administration (FDA) in 2012 also showed the varying occurrence of CIE in patients from different age group and renal status.[14]

Measurement of serum cefepime to predict the neurotoxicity has also been studied. Some early reports suggested neurotoxicity can be expected when the serum level exceeds 22mg/L and the level needed for harm ranges from 2.1 to 18.5 mg/L.[15] Some recent prospective studies in 2017 have suggested neurotoxicity associated with cefepime at concentrations exceeding 35mg/L.[16] The facility to measure serum cefepime level is not readily available in our setting; therefore, we need to have a high index of suspicion based on the clinical manifestations and EEG findings. Apart from the toxic threshold of cefepime concentration, other factors that cause alteration in the blood-brain barrier such as inflammatory conditions, severe sepsis, toxins, metabolic disorder; together with an underlying renal dysfunction has the likelihood to contribute to its neurotoxic potential. In patients with normal renal function, cefepime is eliminated in more than 80% of cases by urine, with a half-life of 2-2.5 hours. In a patient with renal failure and creatinine clearance <10ml/min, the half-life of cefepime is 5 times higher from 2.3 to 13.5 hours and sometimes even up to 22 hours.[17] Cefepime is dialyzable and up to 70% of a given dose can be removed during a 3-hour hemodialysis session.[18]

Haemodialysis therapy has been found to give a good prognosis in patients with CIE. Chatellier et al. reported a series of five cases, all treated with urgent haemodialysis, with full recovery in four cases. Delay in diagnosis in the fifth case could be the reason for the patient's

Table 1. Clinical characteristics and recommended treatment for CIE.

Risk Factors	Signs and symptoms	EEG Characteristics	Treatment
Renal dysfunction Critical illness Altered BBB Older age Drug overdose	Altered mental status Reduced consciousness Confusion Myoclonus Aphasia Seizures	Triphasic waves - multifocal sharp waves - Non-convulsive SE - Generalised slowing - Myoclonic SE	Drug's discontinuation Haemodialysis Benzodiazepine*

*EEG: Electroencephalography, BBB: Blood-brain barrier, SE: Status epilepticus. *for EEG abnormalities/seizure activity associated with toxicity*

death.[18] Haemodialysis seems to be favourable because of its rapid action to clear the drug from circulation. A good understanding of the clinical course and manifestations of CIE may facilitate earlier identification and prompt treatment.[19] However, symptoms may be delayed with a median onset of 4 days after the initiation of the drug. (**Table 1**)

Even though neurotoxicity with cefepime is most commonly occurs when inappropriate doses are administered to patients with renal dysfunction, there are new and emerging evidence that indicate neurotoxicity can happen in patients receiving proper dose adjustments and also in those with normal renal function.[20] The use of alternative antibiotics should be considered for those patients who are at risk of neurotoxicity, at the same time recognizing the potentials emergence of antibiotic resistance. If substituting the antibiotics is not a choice, close clinical monitoring is warranted. Symptoms of CIE can be delayed and progressive, but clinical improvement usually is seen following drug cessation, treatment of epileptiform activity and also drug removal via hemodialysis. In this case, we illustrated the development of CIE in a patient with acute on CKD. However, despite adequate dose adjustment, our patient developed clinical features of CIE after three days of therapy. With a prompt diagnosis of CIE, immediate withdrawal of the drug and urgent hemodialysis showed good clinical outcome for this lady.

CONCLUSION

Recognising cefepime as a source of neurotoxicity can be a challenge given the clinical picture is often clouded by accompanying causes of encephalopathy such as metabolic disturbances, infection, uraemia, and hepatic encephalopathy. For this reason, a heightened index of suspicion is required when treating patients with or without renal impairments, even when cefepime dose is appropriately adjusted.

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