

Relato de CASO

Cefepime encephalopathy and normal renal function

Encefalopatia Induzida por Cefepime em um Paciente com Função Renal Normal

Thiago Cardoso Vale¹

Juliana Cunha²

Antônio Vaz de Macedo³

Breno Franco Silveira Fernandes⁴

Antônio Lúcio Teixeira⁵

Abstract

Background: Several cases of cefepime neurotoxicity have been reported. Herein reported is a case of cephalosporin-associated neurotoxicity in a patient with normal renal function. **Case report:** A 64-year-old woman with a history of post-transplantation chronic myeloid leukemia was admitted to hospital due to hyporexia, fever, productive cough and mild dyspnea. Initial blood screen revealed pancytopenia and a normal renal function. Intravenous cefepime was empirically started and after 40 hours the patient developed sudden mental confusion. Neurological examination was normal. Cranial computed tomography and brain magnetic resonance scans were normal. Electroencephalography showed triphasic waves of diffuse slowness without ongoing epileptic activity. Lumbar puncture was normal. Cefepime neurotoxicity was promptly considered and antibiotics were switched to piperacillin and tazobactam. After five days, the patient recovered completely with remission of myoclonus. **Conclusions:** Awareness should be given to possible central nervous system complications induced by cefepime, especially in the elderly, even without renal failure.

Keywords: cephalosporins; cefepime; encephalopathy.

Resumo

Introdução: Existem vários relatos de casos de toxicidade do sistema nervoso central induzida pelo cefepime. Relata-se um caso de toxicidade do sistema nervoso central associada ao uso de uma cefalosporina em um paciente com função renal normal. **Relato do caso:** Uma mulher de 64 anos com história de transplante de medula óssea devido a leucemia mielóide crônica foi admitida ao hospital devido a hiporexia, febre, tosse produtiva e dispnéia leve. Os exames laboratoriais de rotina demonstraram pancitopenia e função renal normal. O cefepime intravenoso foi empiricamente iniciado e, após 40 horas da administração, o paciente apresentou quadro súbito de confusão mental. Exame neurológico foi normal, assim como a tomografia computadorizada craniana e a ressonância magnética encefálica. O eletroencefalograma demonstrou ondas trifásicas de lentificação difusa sem evidência de atividade epileptiforme. O líquido estava normal. A toxicidade do sistema nervoso central pelo cefepime foi rapidamente considerada e o antibiótico foi trocado para piperacilina e tazobactam. Após cinco dias, o paciente apresentou recuperação completa com remissão da mioclonia. **Conclusão:** Deve-se dar atenção às possíveis complicações do sistema nervoso central induzidas pelo cefepime, especialmente em idosos, mesmo sem insuficiência renal.

Palavras-chave: cefalosporina; cefepime; encefalopatia.

¹MD, Neurology Division, University Hospital, Federal University of Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil. Address: Thiago Cardoso Vale: Hospital das Clínicas - Avenida Professor Alfredo Balena 110 / Terceiro Andar - Ala Oeste (Serviço de Neurologia) - CEP 30130100 - Santa Efigênia - Belo Horizonte (Minas Gerais), Brasil. Email: thiagocardosovale@hotmail.com; Phone: 55-31-9616-7905.

²Medicine student, Federal University of Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil. Address: Juliana Cunha: Hospital das Clínicas - Avenida Professor Alfredo Balena 110 / Terceiro Andar - Ala Oeste (Serviço de Neurologia) - CEP 30130100 - Santa Efigênia - Belo Horizonte (Minas Gerais), Brasil. Email: ju_scunha@yahoo.com.br; Phone: 55-34-8402-0016.

³MD, Haematology Division, Bone Marrow Transplantation Unit, University Hospital, Federal University of Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil. Address: Antônio Vaz de Macedo: Hospital das Clínicas - Avenida Professor Alfredo Balena 110 / Nono Andar - Serviço de Transplante de Medula Óssea - CEP 30130100 - Santa Efigênia - Belo Horizonte (Minas Gerais), Brasil. Phone: 55-31-8411-3073; Email: antoniovmac@hotmail.com; Phone: 55-31-8802-8700

⁴MD, Neurology Division, University Hospital, Federal University of Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil. Address: Breno Franco Silveira Fernandes: Hospital das Clínicas - Avenida Professor Alfredo Balena 110 / Terceiro Andar - Ala Oeste (Serviço de Neurologia) - CEP 30130100 - Santa Efigênia - Belo Horizonte (Minas Gerais), Brasil. Email: brenofranco@gmail.com; Phone: 55-31-3409-9417.

⁵MD, PhD, Department of Internal Medicine, Neurology Division, Faculty of Medicine, Federal University of Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil. Address: Antônio Lúcio Teixeira: Departamento de Clínica Médica. Faculdade de Medicina - Universidade Federal de Minas Gerais (UFMG). Avenida Professor Alfredo Balena 190 Bairro Santa Efigênia. CEP 30130-100 - Belo Horizonte (MG), Brasil. Phone: (55-31) 3409-9417; Email: altextr@gmail.com

I confirm that the study has received the patient consent for publication. There are no competing interests to declare. We declare no financial support.

Correspondence address: Thiago Cardoso Vale, Hospital das Clínicas - Universidade Federal de Minas Gerais, Avenida Professor Alfredo Balena, 110 - Bairro Santa Efigênia, CEP 30130-100 - Belo Horizonte (MG), Brazil.
Email: thiagocardosovale@hotmail.com / Phone: 55-31-3409-941

Introduction

Cefepime is a fourth-generation cephalosporin active against both gram-positive and gram-negative infections. Several cases of cefepime neurotoxicity have been reported with an estimated prevalence of about 3%¹. The main predisposing factors are pre-existing central nervous system (CNS) abnormalities and renal impairment with excessive dosing of the antibiotic^{1,2}. Except for three previous reports³⁻⁵, cephalosporin-associated neurotoxicity has been described in patients with renal failure or overdose due to prolongation of the half-life. Herein reported is the fourth case of cephalosporin-associated neurotoxicity in a patient with normal renal function presenting with encephalopathy and myoclonus.

Case Report

A 64-year-old woman with a history of chronic myeloid leukemia treated with bone marrow transplantation. During the post-transplant immunosuppressive period, the patient presented with herpetic and cytomegalovirus infections. After a year and a half of transplantation, the patient was readmitted to hospital due to hypoxemia, fever and productive cough and mild dyspnea. Initial blood screen revealed pancytopenia (platelet count of 8.000/mm³, hemoglobin count of 8.9 mg/dL and neutrophil count of 1190 cells/mm³) and a normal renal function (urea and creatinine levels at, respectively, 49 mg/dL and 1 mg/dL). Creatinine clearance was at 60 ml/kg/min. Intravenous cefepime (2 g every 8 hours) was empirically started and after 40 hours the patient developed a sudden confusional state with generalized myoclonus. She became unresponsive while alert and had intermittent obtundation. She did not answer questions or follow commands. Except for brisk generalized tendon reflexes, the neurological examination was normal. Cranial computed tomography scan and brain magnetic resonance

imaging were normal. Electroencephalography showed triphasic waves of diffuse slowness without ongoing epileptic activity. Lumbar puncture yielded 1 white blood cell/dL, 65 proteins/dL and 60 mg/dl of glucose levels. Culture, gram-stain and venereal disease research laboratory were negative. Blood and cerebrospinal fluid Herpes simplex polymerase chain reactions were negative. Cefepime neurotoxicity was promptly considered and antibiotics were switched to piperacillin and tazobactam. Acyclovir was also empirically started due to the possibility of herpetic encephalopathy. After five days, the patient recovered completely with remission of myoclonus. She progressively recovered from her pneumonia and was discharged after further neurological observation.

Discussion

Our case illustrates that cefepime neurotoxicity, herein illustrated by encephalopathy with myoclonus, can occur even at presence of normal renal function. Three case reports have already described cefepime-related CNS complications in patients with normal renal function. Although we looked for other causes of encephalopathy, such as electrolyte disorders, and other metabolic alterations, infections, cerebral hypoxia, tumors, stroke, alcohol withdrawal, and use of other epileptogenic medications, only cephalosporins were temporally related to the appearance of the clinical picture.

The mechanisms involved in the development of cefepime neurotoxicity have not been clearly understood and no consistent hypothesis was found in literature to explain its pathophysiology in patients with normal renal function.^{2,5} We should be aware of the possible CNS complications (non-convulsive status epilepticus or encephalopathy) induced by cefepime and other cephalosporins, especially in the elderly, critically ill patients, even without renal failure.

References

1. Neu HC. Safety of cefepime: a new extended-spectrum parenteral cephalosporin. *Am J Med* 1996;100:68S-75S.
2. Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. *Ann Pharmacother* 2008; 42:1843-50.
3. Lin CM, Chen YM, Po HL, Hseuh IH. Acute neurological deficits caused by cefepime: a case report and review of literature. *Acta Neurol Taiwan* 2006;15:269-72.
4. Capparelli FJ, Diaz MF, Hlavnika A, Wainsztein NA, Leiguarda R, Del Castillo ME. Cefepime and cefixime-induced encephalopathy in a patient with normal renal function. *Neurology* 2005;65:1840.
5. Maganti R, Jolin D, Rishi D, Biswas A. Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. *Epilepsy Behav* 2006;8:312-4.