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Cefepime-induced neurotoxicity in a patient with renal dysfunction: a case report

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Abstract

Cefepime is an antimicrobial widely used in the hospital environment. During the development phases, the drug proved to be safe and, therefore, was approved and marketed. After the commercialization of cefepime, case reports involving a serious adverse reaction were emerging. Cefepime-Induced Neurotoxicity (CIN) is a reaction that occurs most often in patients with renal dysfunction, damage to the blood-brain barrier or advanced age. Dose adjustment should be made according to creatinine clearance in order to prevent adverse reaction. Among the symptoms are drowsiness, tremors, myoclonus, agitation, lowered level of consciousness, convulsions and coma. The electroencephalogram can be used to aid in the diagnosis, but it is not specific for this condition. In this article, we present a case report of a 52-year-old woman with acute renal failure who presented CIN after using cefepime, despite dose adjustments according to renal function. The patient presented the symptoms even after discontinuing the medication and hemodialysis did not reverse the condition. The patient's physiological characteristics may have contributed to the outcome of the case. The description of CIN cases in the literature is important for a better understanding of the pathophysiology that involves the adverse reaction and prevention of new cases.

Keywords: cephalosporins, adverse effect, encephalopathy, acute kidney injury, hemodialysis.

Neurotoxicidade induzida por cefepima em paciente com disfunção renal: um relato de caso

Resumo

O cefepima é um antimicrobiano extensamente utilizado no ambiente hospitalar. Durante as fases de desenvolvimento o medicamento se demonstrou seguro e por isso foi aprovado e comercializado. Após a comercialização do cefepima, relatos de casos envolvendo uma reação adversa grave foram surgindo. A Neurotoxicidade Induzida por Cefepima (NIC) é uma reação que ocorre, na maioria das vezes, em pacientes que apresentam disfunção renal, danos na barreira hematoencefálica ou com idade avançada. O ajuste de dose deve ser feito conforme a depuração de creatinina, a fim de prevenir a reação adversa. Dentre os sintomas estão sonolência, tremores, mioclonias, agitação, rebaixamento do nível de consciência, convulsões e coma. O eletroencefalograma pode ser utilizado para auxiliar no diagnóstico, mas não é específico para essa condição. Neste artigo apresentaremos um relato de caso de uma mulher de 52 anos, com insuficiência renal aguda, que apresentou a NIC após o uso de cefepima, apesar dos ajustes de dose conforme função renal. A paciente apresentou os sintomas mesmo após a suspensão do medicamento e a hemodiálise não reverteu o quadro. Características fisiológicas da paciente podem ter contribuído para o desfecho do caso. A descrição dos casos de NIC na literatura é importante para melhor compreensão da fisiopatologia que envolve a reação adversa e prevenção de novos casos.

Palavras-chave: cefalosporinas, efeito adverso, encefalopatia, lesão renal aguda, hemodiálise.

Introduction

Cefepime is a fourth-generation cephalosporin widely used due to its broad spectrum of action (gram-negative and gram-positive). In addition to that, it has activity against *Pseudominas aeruginosa* and stability against *Enterobacteriaceae* degradation enzymes (AmpC β-lactamase)[1]. This antimicrobial is the first line to treat various infectious diseases such as febrile neutropenia, hospital-acquired pneumonia, bacterial meningitis, complicated and uncomplicated urinary tract infections, skin and soft tissue infections, and intra-abdominal and gynecological infections[2].

The data related to cefepime safety were favorable and resulted, with the health authority, in its approval and commercialization. The rate of neurotoxic events was relatively low and there were no clear causal relationships. However, over the years, a series of case reports was published relating use of antimicrobials to patients' altered mental status[2]. Cefepime-Induced Neurotoxicity (CIN) is reported as a toxic encephalopathy or non-convulsive status epilepticus. Among the manifestations we can mention the following: seizure, non-convulsive seizure, myoclonus, tremors, drowsiness, altered mental status with mental confusion or disorientation, agitation, hallucinations, lowered level of consciousness and coma[1,3].

In 2011, the Food and Drug Administration (FDA) in the United States of America (USA) concluded that there was no significant association between cefepime use and increased mortality[4]. However, there are controversial data and recent studies indicate the relationship between its use and patient mortality[5].

We will present a single CIN case in a 52-year-old woman who used the antimicrobial drug during renal dysfunction.

Case report

A 52-year-old woman with a history of follicular lymphoma treated with bone marrow transplantation that presented Graft-versus-Host Disease (GVHD) as complication. During monitoring of the post-transplantation period, the patient started with severe diarrhea, associated with vomiting and abdominal distension. On admission for hospitalization, she was dehydrated and with Stage 2 Acute Renal Failure (ARF), classified according to the Brazilian Society of Nephrology, 2007[6]. Basal creatinine (Cr) 0.76 mg/dL, admission Cr 1.67 mg/dL. Cefepime was initiated at a dosage of 2 g every 12 hours due to the patients' rapid clinical deterioration and presence of fever. After 24 hours, the cefepime dose was adjusted to the patient's renal function (1 g every 24 hours). The Glasgow scale on admission was 15. Three days after initiating the antimicrobial, the patient became drowsy and progressed to deteriorated renal dysfunction (Cr 3.20 mg/dL) and oliguria (decreased diuresis), configuring Stage 3 ARF. On the same day, she presented lowered level of consciousness and was referred to the Intensive Care Unit (ICU) with Glasgow 12, where she reached Glasgow 3 and required intubation. The possibility of infection was ruled out due to the absence of microorganisms in cultures and to fever cessation. Cefepime was discontinued. The medication was adjusted according to the Cockroft-Gault (CG) formula during its use. The electroencephalogram (EEG) performed on admission to the ICU showed diffuse cerebral dysfunction, without non-convulsive status. After five days, a new EEG was performed, which identified permanence of diffuse cerebral dysfunction, now more evident on the right cerebral hemisphere, with presence of triphasic waves that suggest drug-induced metabolic or toxic encephalopathy[7]. Cefepime serum monitoring was not available. The patient remained in a comatose state, evolving with a need for hemodialysis, undergoing a session on the 6th day after discontinuing cefepime, without reversion of the symptoms. Two days later, a new session was scheduled but the patient evolved with hemodynamic instability during the procedure, making it impossible to perform the session. The patient died following day.

Discussion

The neurotoxic effect of cefepime was first reported in 1996[8]. Its pathophysiology can be related to inhibition of gamma-aminobutyric acid (GABA) release or to inhibition of GABA-A receptors[9]. The brain uses GABA as a neuronal excitability and continuous activity modulator, controlling the generation of membrane potential oscillations[10]. Therefore, reduced GABAergic tone is seen as a proconvulsant, whereas increased GABAergic tone generally has an anticonvulsant effect[11].

The main risk factor for neurotoxicity is renal dysfunction and non-adjustment of the cefepime dose, which leads to accumulation of the drug in the body[12]. Cefepime depuration is 85% renal in the unaltered form, with a half-life of 2 hours. With renal dysfunction, half-life of the drug can reach 13.5 hours[13]. According to the manufacturer, the cefepime dose should be adjusted according to the creatinine clearance rate, with adjustments recommended starting with a creatinine clearance (CrCl) value of less than 50 mL/min. Dose adjustment based on CrCl should be used in cases where renal function is normal and stable[14].

CIN can also occur in cases where there is dose correction according to renal function or even in the presence of normal renal function.

In a study carried out between 2008 and 2009 at the Porto Alegre Clinical Complex Hospital (*Hospital de Clínicas de Porto Alegre*, HCPA), 1,035 patients using cefepime were studied[15]. The cumulative incidence of CIN was 1.9% in the selected population, whereas in the population with Glomerular Filtration Rate (GFR - According to the Modification of Diet in Renal Disease formula - Simplified MDRD) it was ≥ 60 mL/min 1%, from 59 to 30 mL/min: 2.7%, from 15 mL/min to 29 mL/min: 5.4% and, in patients with GFR <15, mL/min: 7.5%. These results show that the incidence of CIN increases with loss of renal function[15].

The renal function estimates based on creatinine clearance calculations are only validated for stable renal function. In cases where ARF occurs or where renal function is rapidly changing, these measurements may be delayed by up to 36 hours, significantly overestimating or underestimating current renal function. It is recommended to choose not to adjust the antimicrobial to avoid underdoses. β-lactams can wait up to 48 hours before being adjusted[18].

Although there is no consensus regarding cefepime serum monitoring, it is believed that the threshold is around 20 mg/L[16]. Some data suggest that neurotoxicity can even be associated with minimum cefepime concentrations above 35 mg/L[3]. Serum monitoring can contribute to safe use of the drug, requiring further studies to define the therapeutic limits[12].

In addition to renal dysfunction, patients with damage to the Blood-Brain Barrier (BBB) integrity due to systemic inflammation, uremia or Central Nervous System (CNS) infection are more prone to CIN due to greater penetration of cefepime[16]. A mean of 10% of serum cefepime crosses the BBB; however, changes in renal function, decreased binding to plasma proteins and accumulation of organic acid can lead to an increase of up to 45%[3]. The patients' age can also be considered a risk factor, aged patients are more likely to have CIN than younger patients[7,9].

Development of symptoms related to cefepime neurotoxicity occurs on average within 4 to 5 days of therapy initiation and resolves within 3 to 4 days of treatment discontinuation[7]. Patients

with changes in the sensorium, behavior or even cognition can be considered as suspects for CIN[15]. Electroencephalograms can be performed to confirm the diagnosis and even monitor the patient. CIN can disorganize a patient's baseline rhythm in different ways, and it can be identified before onset of the symptoms. Neurotoxic substances initially cause diffuse cortical neuronal dysfunction. With such deterioration, the dominant frequencies pass from the theta band (4-7 Hz) to the delta band (1-3 Hz), causing a slowdown in the EEG and leading to a moderate to severe decrease in the patient's level of consciousness. In their EEGs, most of the patients with severe CIN present acute waves with triphasic morphology (0.5-2 Hz) in the frontal region, diffusely distributed and bilateral[15]. Although the EEG findings are useful, they are not specific to cefepime alone and may be due to other causes such as metabolic encephalopathies and brain damage caused by anoxia[7].

In some patients, findings consistent with non-convulsive status epilepticus, myoclonic status epilepticus and focal sharp waves can be seen[3].

The definitive treatment for CIN is cefepime discontinuation[16]. In a meta-analysis, the most common intervention was withdrawal (81%) or interruption of treatment with dose reduction (4%), leading to clinical improvement in 90% of the patients within 3 days[3].

Hemodialysis rapidly removes cefepime from the blood and cerebrospinal fluid and can be used to accelerate recovery, especially when it is life-threatening[17]. In a single 3-hour session, it is possible to remove 70% of the dose due to low binding to plasma proteins (20%)[13], low molecular weight and low distribution volume (18 L or 0.26 L/Kg in adults)[13,16].

Conclusion

Although dose adjustment was performed based on the patient's CrCl and corrected for renal dysfunction, the patient had an adverse reaction. Even after discontinuing the drug and attempting hemodialysis, there were no changes in the patient's level of consciousness. The patient received the dose without adjustments for 24 hours, ensuring that the serum level was achieved during this period. Subsequently, the adjustment was made for the patient's safety, considering that her renal function continued to decline. Other factors such as the underlying disease, GVHD, renal dysfunction, intolerance to the tube-administered diet, inflammatory status and even the reasons that led to hospitalization, may have contributed to evolution of the condition and to the patient's unfavorable outcome, even though the professionals had carried out the appropriate procedures for the case.

Describing CIN cases is important to improve understanding of the pathophysiology of the adverse reaction in order to make it preventable.

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The authors declare no conflicts of interest.

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