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Myoclonic status secondary to cefepime toxicity

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Abstract

Adverse drug reactions (ADRs) are defined as any harmful and unwanted effect that occurs at doses used for therapeutic or prophylactic purposes, being a frequent cause of mortality and morbidity. We present the case of a 36-year-old female patient with a history of HIV without antiretroviral therapy, in stage B2 (undetectable viral load, CD4 208) who was admitted due to emergency dialysis secondary to obstructive nephropathy due to ureterolithiasis. During hospitalization, she presented diarrheal episodes with isolation of Klebsiella pneumoniae in stool culture, which is why the treating service started therapy with cefepime not adjusted to renal function. Subsequently, she presented a sudden picture of altered state of consciousness, myoclonic and myoclonic status, for which extension studies were performed, with CT, electrolytes, glucometry, which was normal, and lumbar puncture where infection by opportunistic germs was ruled out. Given the suspicion of cefepime toxicity, it was decided to suspend it and ultrafiltration was carried out with complete improvement of the neurological picture 2 days later, for what we consider neurotoxicity secondary to antimicrobial therapy.

Introduction

Every year, more than 1,000 patients are hospitalized due to adverse drug effects, mostly antimicrobial therapies, since they cause cardiac, renal, hepatic, and neurological toxicity (1). In Europe it is estimated that 5% of all hospitalizations are secondary to a drug reaction and close to 5% of hospitalized patients present some type of response to drugs during their hospital stay. (2)

RAMS are classified as predictable (type A) or unpredictable (type B) depending on their origin ; predictable reactions are dose-dependent, related to the drug's mechanism of action, and occur in previously healthy individuals ; on the other hand, type B reactions are not associated with the dose and occur in susceptible people, regardless of their mechanism of action, the latter include intolerance, idiosyncratic reaction, and allergy. (2,3) Beta-lactams and glycopeptides are the most frequent causes of adverse reactions. (4)

Cefepime is a beta-lactam, classified as a fourth-generation semisynthetic cephalosporin, generally very well tolerated and has a lower incidence of serious adverse effects compared to other cephalosporins. (5) Cephalosporins have a lower degree of epileptogenic activity due to their different chemical structure than other penicillins, however, in higher doses they reach high concentrations in the blood, cerebrospinal fluid and brain, especially when there is impaired renal function. (5,6)

Its route of excretion is mainly renal, which requires dose adjustment to a glomerular filtration rate of less than 50 ml/min, since its accumulation can generate adverse effects, among which the most important is neurotoxicity,

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which is manifested as altered mental status (80%) delirium (47%) myoclonus (40%) and convulsive status explained by the inhibition of the binding of gamma-aminobutyric acid (GABA) to its GABA-A receptor, leading to hyperexcitability of neurons and depolarization of the postsynaptic membrane, lowering the seizure threshold.(6,7) The GABA A receptor has anxiolytic, anticonvulsant, amnesic, hypnotic, euphoric, and muscle relaxant properties. (7,8)

Cefepime toxicity was evidenced for the first time in 1999 with a latency in the development of symptoms of 1-10 days, resolving them within 2-7 days after discontinuation of the drug, early diagnosis being the key to a neurological outcome. favorable. (9) Situations such as hypoalbuminemia and renal impairment extend the half-life of the drug, precipitating serum concentrations. This drug has a low protein binding of 16-20% and 80% renal excretion, so hemodialysis therapy is the choice to reverse toxicity secondary to cefepime (3). The diagnosis of neurological adverse effects is clinical, however, the electroencephalogram is useful in patients with metabolic encephalopathy, the alterations are usually bilateral and symmetrical, it will help us to determine non-convulsive status epilepticus and myoclonic status epilepticus. (3,4,15)

Below is a case report of a patient with myoclonic status secondary to the use of cefepime.

Clinical case

A 45-year-old female patient, diagnosed with HIV for 2 years in stage B2 without antiretroviral treatment (CD4 208) who was admitted due to emergency dialysis secondary to obstructive nephropathy due to ureterolithiasis. During his hospitalization, he presented feverish peaks associated with acute diarrheal syndrome with isolation in stool culture of Klebsiella pneumoniae, a producer of ESBL (extended-spectrum beta-lactamase), for which they began therapy with cefepime at a dose of 2 gr IV every 8 hours, however, 4 days after the hospitalization. initiation of antibiotic therapy presents altered mental status due to fluctuations in the state of consciousness associated with myoclonus. On neurological physical examination, the patient had global aphasia, mild hypotonia, diffuse clonic movements predominantly in the upper and distal limbs, weakness Left with normal reflexes. A CT scan of the head and a magnetic resonance imaging of the brain were performed without relevant alterations and a lumbar puncture ruled out neuroinfection (white blood cells in CSF 2) without hypoglycorrhachia (glucose 60 - relation to serum glucose 0.5) and mild hyperproteinorrachia (protein 52) however before the Base immunosuppression, studies of opportunistic germs in CSF were started, which was ruled out (ADA 0.9 negative, non-reactive VDRL, Cryptococcus antigen, PCR for M. tuberculosis, FILM array negative meningeal panel, culture for common germs, gram, KOH, ink china negative) also with urinary antigen for Histoplasmosis in urine negative

Electrolytes, urea nitrogen and blood glucose were requested, which were normal; sodium 137 mmol/L, potassium 4.7 mmol/L, chlorine 107 mmol/L, blood glucose 118 mg/dL, BUN 16 mg/dL. An electroencephalogram of wakefulness and sleepiness was performed, which evidenced an abnormal result, with slowing of the background rhythms and occasionally, it showed a periodic pattern of triphasic morphology, suggesting a mild diffuse brain disorder, corresponding to encephalopathy. No discharges were observed. epileptiformes or focal signs in the present study.

Therefore, we consider that the neurological alterations were secondary to cefepime toxicity given the supra-therapeutic doses received in the context of kidney disease, which is why ultrafiltration therapy was suspended and indicated with total improvement of symptoms after two days.

Discussion

Our case is that of a female patient with a history of glomerulopathy, nephrolithiasis, and recurrent urinary tract infections that led to the need for dialysis support. In patients with clearance less than 50 ml/min, the appropriate doses of cefepime are 2 gr IV every 12 hours and in rates less than 15 ml/min the dose should be 500 mg IV per day, however, in the presence of pathogens. With high MICs (minimum inhibitory concentration), the administration of higher doses, continuous or prolonged infusion may be necessary to ensure microbiological success, exposing them to undesired effects, which is why their serum levels are monitored (11,12,13). .

Encephalopathy is a brain dysfunction of different etiologies that is characterized by changes in alertness and higher mental functions. In our case, the patient presented a metabolic encephalopathy evidenced in the results of the electroencephalogram associated with the clinic, secondary to the toxic accumulation of cefepime. Although its adverse effects are rare, the renal deterioration conditioned the drug to reach supra doses. therapeutic at the brain level generating distal myoclonus predominantly in upper limbs, this being characteristic of beta-lactam toxicity, he also presented confusional syndrome which is explained in the literature by the release of excitatory amino acids and cytokines that induce endotoxins with glutaminergic mechanisms upon exposure to the drug (13-14).

The case exposes a patient with HIV who, although the initial symptoms presented could be explained by infections generated by opportunistic germs, a lumbar puncture was

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performed which ruled out neuroinfection. We ruled out infection by M. tuberculosis (ADA and PCR in CSF negative), cerebral cryptococcosis (Cryptococcus antigen in CSF), syphilis (VDRL), disseminated Histoplasmosis (urinary Histoplasma antigen), bacterial or viral meningoencephalitis (gram, culture and FILM array). negative) so within the differentials HIV encephalopathy was considered, however given the characteristics of the picture, it was determined that the cause of the neurological symptoms were secondary to the toxic levels of cefepime.

To reverse the adverse effects secondary to the use of cefepime, it is necessary to suspend it and in severe or refractory cases, dialysis therapy is indicated. In relation to the management indicated in our case, it required suspension of the antibiotic and ultrafiltration therapy, which allowed the rapid reduction of cephalosporin levels in CSF and blood, which were not measured due to the non-availability, reducing cerebral toxicity with improvement of the symptoms.

Table 1: *Infections ruled out at the CNS level.*

Infecciones	Agente etiológico	Paraclínicos
Tuberculosis meníngea	*Mycobacterium tuberculosis*	ADA 0.9 (negativo), PCR negativa
Neurosifilis	*Treponema pallidum*	VDRL negativo
Criptococosis meníngea	*Cryptococcus neoformans*	Antígeno en LCR/FILM array negativo
Infecciones virales	Cytomegalovirus, Enterovirus, Herpes simple 1 y 2, Herpes virus 6, Varicela zoster	FILM array negativo
Infecciones bacterianas comunes	*Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactie, pneumoniae, Haemophilus influenzae.*	FILM array negativo

Conclusions:

Beta-lactams are a frequent cause of adverse effects, especially allergies and damage to the nervous system with significant renal excretion, so dose adjustment based on renal function is recommended. Caution should be exercised with the use of cefepime for long periods of time and in patients at high risk of neurological complications.

In the aforementioned case, neurotoxicity secondary to the use of cefepime was documented in a patient with chronic kidney disease with doses not adjusted to the renal filtration rate, where there was total improvement in symptoms upon withdrawal of the antibiotic and dialysis therapy. The diagnosis of metabolic encephalopathy was confirmed by electroencephalogram results. Within the differential diagnoses, infections due to opportunistic germs, hydroelectrolytic disorders, sepsis, cerebrovascular disease and uremia were excluded.

Conflicts of interest: There are no potential conflicts of interest related to the contents of this article.

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