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Encephalopathy Tango: When Beta-Lactam Antibiotics Waltz with GABA Receptor

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Encephalopathy Tango: When Beta-Lactam Antibiotics Waltz with GABA Receptor

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Abstract

Beta-lactam antibiotics are a class of drugs that are widely used to treat a variety of infections. They are generally well-tolerated, but they can cause a variety of side effects, including allergic reactions, acute interstitial nephritis (AIN) and neurotoxicity.

We present a patient who developed neurotoxicity after being treated with cephalosporin and carbapenem antibiotics. A 76-year-old female was admitted to the hospital with osteomyelitis of the right foot. She was initially treated with cefepime and daptomycin. She was discharged and then began to experience delirium with visual hallucinations and acute kidney injury. After common causes of confusion were excluded, the patient was believed to have cefepime-related neurotoxicity. She was switched to ertapenem and the delirium was resolved. A few days later Ertapenem was then changed to meropenem based on pseudomonas found in culture. The patient again started to develop delirium after starting the meropenem, and the cause was believed to be meropenem-related neurotoxicity. Her confusion resolved after switching antibiotics to piperacillin-tazobactam.

Beta-lactam antibiotics are associated with neurotoxicity, and risk is increased with the geriatric population, female sex, and neurological and kidney diseases. Both Cefepime and Meropenem can cause neurotoxicity and delirium. The mechanism of neurotoxicity is believed to be due to Gamma-aminobutyric acid (GABA) antagonism; Carbapenem binds to GABA receptors while Cefepime decreases GABA release from nerve terminals. Important steps in treating antibiotic-associated neurotoxicity are the withdrawal of the offending drug, use of benzodiazepine, and intermittent dialysis if no response is observed after discontinuation of the offending medication.

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Conflict of Interest Statement

no conflict of interest

Cover Page Footnote

Special thanks to Tamer Salhab, MD, for his efforts in creating the graph.

CASE REPORT

Encephalopathy Tango: When Beta–Lactam Antibiotics Waltz with GABA Receptor

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Abstract

Beta-lactam antibiotics are a class of drugs that are widely used to treat a variety of infections. They include penicillins, cephalosporins, carbapenems, and monobactams. Beta-lactam antibiotics are generally well-tolerated, but they can cause a variety of side effects, including allergic reactions, acute interstitial nephritis (AIN) and neurotoxicity.

In this case report, we present a patient who developed neurotoxicity after being treated with a cephalosporin antibiotic. The patient's symptoms resolved after the cephalosporin was discontinued. However, the symptoms recurred after the re-introduction of a carbapenem antibiotic. A 76-year-old female with no history of kidney disease was admitted to the hospital with osteomyelitis of the right foot. She was initially treated with cefepime and daptomycin. She was discharged to a nursing home and then began to experience delirium with visual hallucinations and acute kidney injury. After common causes of confusion were excluded, the patient was believed to have cefepime-related neurotoxicity. She was switched to ertapenem and delirium and hallucinations resolved. A few days later ertapenem was then changed to meropenem based on pseudomonas found in culture. The patient again started to develop delirium within 48 hours of beginning the meropenem, and the cause was believed to be meropenem-related neurotoxicity. Her confusion resolved after stopping meropenem and switching antibiotics to piperacillin-tazobactam. Beta-lactam antibiotics are associated with neurotoxicity, and risk is increased with the geriatric population, female sex, and neurological and kidney diseases. Cefepime-related neurotoxicity can also occur in patients with normal kidney function. Both Cefepime and Meropenem can cause neurotoxicity and delirium. The mechanism of neurotoxicity is believed to be due to Gamma-aminobutyric acid (GABA) antagonism; Carbapenem binds to GABA receptors through the C2 side chain, and the incident of neurotoxicity is related to its alkalinity which leads to solubility across biological membranes. Cefepime alters lipid metabolism in the corpus striatum and decreases GABA release from nerve terminals. Important steps in treating antibiotic-associated neurotoxicity are the withdrawal of the offending drug, use of benzodiazepine, and intermittent dialysis if no response is observed after discontinuation of the offending medication.

Avoidance of antibiotics with GABA antagonism may help prevent the recurrence of neurotoxicity in a patient who has developed neurotoxicity related to Cefepime.

Keywords: Neurotoxicity, Cefepime, Meropenem, GABA receptor

1. Introduction

Antibiotic resistance is a clinical challenge nowadays, and clinicians sometimes have limited options for covering microorganisms. Therefore broad-spectrum antibiotics, such as carbapenems, have been used more often during the past decade, with an expected 200% increase in consumption in 2030.¹ Antibiotics are life-saving

medications; however, all drugs carry side effects, which adds to the complexity of choosing antibiotics in the appropriate clinical settings.

Beta-lactams are known to cause neurotoxicity or delirium. The most common manifestation of neurotoxicity includes agitation, disorientation, visual and auditory hallucination, and altered sensorium. Seizures are rare, with less than 1% incidence in carbapenem use.² However, seizures

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are the most feared complication due to their mortality risk.

Antibiotics associated with delirium include ertapenem, Cefepime, imipenem, ofloxacin, ceftazidime, clarithromycin, cefaclor, ampicillin-sulbactam, levofloxacin, linezolid, moxifloxacin, azithromycin, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, metronidazole, ciprofloxacin, and cefuroxime. Symptoms usually manifest within four days after starting antibiotics and typically progress upon the continuation of the culprit antibiotic. It usually resolves within two days of discontinuing medication alone or in addition to intermittent dialysis or benzodiazepine.³ We describe an unusual case where a patient developed Cefepime-induced neurotoxicity in the presence of acute kidney injury with resolution after stopping Cefepime. However, neurotoxicity recurred with the subsequent use of Meropenem.

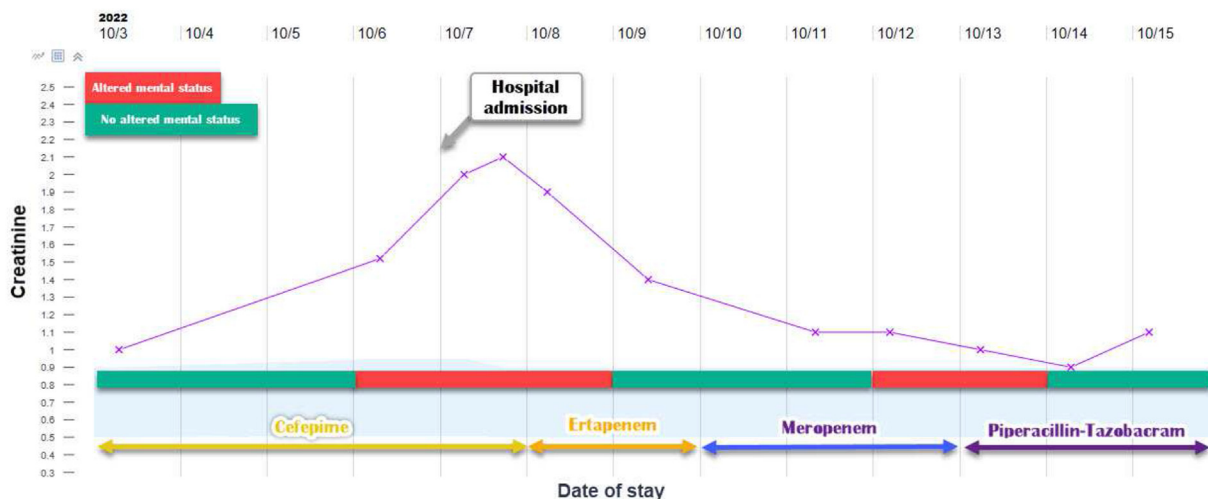
2. Case presentation

A 76-year-old female with a past medical history of ischemic cardiomyopathy, cerebrovascular accident (CVA), bilateral knee replacement, hyperlipidemia, and hypertension was initially admitted to the hospital for left cuboid osteomyelitis and abscess of the left foot. Culture from the biopsy grew multidrug-resistant staphylococcus aureus, pseudomonas, enterobacter, and Serratia. She underwent debridement twice and started on intravenous antibiotics, including Cefepime and daptomycin. She was hospitalized for two weeks, during which antibiotics were continued. Kidney function remained stable, and the patient's mentation was normal during hospitalization. She was discharged

and was planned to continue on Cefepime and daptomycin for a total of six weeks.

She then started to have altered mentation three days after discharge and was readmitted to the hospital. She was hypotensive with systolic blood pressure in the 90s. Blood work also showed acute kidney injury with creatinine increase from 1.0 on discharge to 2.1 mg/dL. The patient reported having decreased oral intake, and the cause of kidney injury was considered prerenal. Laboratory workup was significant for leukocytosis of 14,500/microL with predominant neutrophils at 77%, but CRP and lactic acid levels were normal. Creatine kinase was within normal limits.

She was appropriately resuscitated with intravenous fluid as she was volume-depleted and creatinine improved afterward (Graph 1). Cefepime and daptomycin were initially continued, and the workup for metabolic encephalopathy, including electrolytes, liver function, sepsis workup (lactate, blood, and urine culture, chest X-ray), venous blood gas, and head CT was unremarkable. However her mentation declined during the hospital stay; she became disoriented, agitated, and experiencing visual hallucinations. Medications were reviewed, and due to the possibility of cefepime-induced neurotoxicity, Cefepime was discontinued and replaced with ertapenem. Mentation and renal function improved significantly within two days of cefepime withdrawal. As culture grew pseudomonas, ertapenem was switched to Meropenem to cover for pseudomonas on day three. The Meropenem dose was adjusted based on the glomerular filtration rate (GFR). She started having the same visual hallucinations, disorientation, and agitation on the fourth day of her presentation. Subsequently, Meropenem



Graph 1. Interval graph with creatinine trend and antibiotics during the hospital stay.

was discontinued and started piperacillin-tazobactam. Confusion improved 48 h after meropenem withdrawal, and mentation returned to normal to her baseline at the time of discharge.

3. Discussion

Risk factors for developing beta-lactam-induced neurotoxicity were identified in the literature as old age, female gender, pre-existing neurological disease, and decreased GFR. The median age for developing delirium was 69. Renal dysfunction plays a significant role in neurotoxicity, especially with antibiotics with good blood–brain barrier penetration as Cefepime.³ Data suggested the highest risk factor for developing neurotoxicity is inappropriate dosing in the settings of decreased renal clearance; however, there are also incidents of neurotoxicity in subjects with normal GFR. In one study, nearly one-quarter of subjects with antibiotic-related neurotoxicity received appropriate dosing.² Our patient was started on Cefepime when her GFR was normal while admitted, and her kidney function deteriorated after discharge.

We postulate that her neurotoxicity was potentially preventable by avoiding Meropenem, which contrasts Ferrara et al., who implied Meropenem is a safe option for patients with a history of cefepime-induced neurotoxicity.⁶ Schliamser et al. also identified nephrotoxic drugs and drugs that decrease seizure threshold among risk factors for beta-lactam-induced seizure.⁴ We suggest that a previous history of antibiotic-induced neurotoxicity is among the risk factors for developing repeated neurotoxicity with antibiotics that exhibit GABA antagonism. Another possibility in our patient could be the persistence of Cefepime in the brain despite discontinuation. This possibility is less likely as our patient's symptoms had resolved, and she became symptomatic again only after starting Meropenem.

Cefepime and imipenem carry the same incident of delirium, roughly 9%.⁹ The mechanism of carbapenem neurotoxicity is proposed to be due to GABA A antagonism as described by Norrby et al.⁵ Cross-reactivity between beta-lactam antibiotics is believed to be related to their sidechain similarities. In cephalosporin-allergic subjects, only 1% had cross-reactivity to Meropenem. Carbapenem binds to GABA receptors with its C2 side chain and beta-lactam rings. Different Carbapenems vary in their neurotoxicity rate, which is believed to be due to differences in the side chain. For instance, imipenem is more alkaline in the side chain, resulting in increased incidents of seizures compared to Meropenem.^{7,8} Interestingly, this patient tolerated ertapenem with no mental

status changes despite having meropenem-induced neurotoxicity afterward. One of the possibilities is a delayed reaction that resulted in her behavioral manifestation after starting the meropenem. Having improved kidney function might have also played a role making the subject at a lower risk of developing ertapenem-induced neurotoxicity. Further research is needed to explore the exact pathophysiology of neurotoxicity and whether molecular differences between the same class of antibiotics play a role in predicting side effects.

Cefepime neurotoxicity is not completely understood. The literature suggests GABA receptor antagonism. Cefepime is proposed to work by decreasing GABA release from nerve terminals, potentially lowering the seizure threshold.¹⁰ In animal studies, Cefepime was also found to alter glycerophospholipids in the basal ganglia, possibly leading to neurotoxicity and hallucination.¹¹ Benzodiazepines were also helpful to counteract these symptoms, which adds more convincing evidence to GABA antagonism by Cefepime. Our patient did not need benzodiazepines as she returned to her baseline mentation afterward.

In conclusion, antibiotic-induced neurotoxicity has a broad spectrum of manifestations, initially presenting with altered mentation and can progress to seizures. If symptoms do not resolve with drug withdrawal, it is reasonable to use benzodiazepine and intermittent dialysis in the appropriate clinical settings. Antibiotics' side effects need to be weighed against their benefits. Efforts should be made to avoid drugs with GABA antagonist activity when clinically feasible to avoid recurrent side effects in patients with a previous history of cefepime-induced neurotoxicity.

Financial disclosure

None reported.

Conflicts of interest

The authors report there are no conflicts of interest.

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