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CASE REPORT

Imipenem-Cilastatin-Induced Seizures: A Case Report

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Abstract: ***Background*:** Imipenem-cilastatin, a carbapenem antibiotic, is commonly used for severe bacterial infections. While generally well-tolerated, it can rarely cause central nervous system toxicity, including seizures. We have, herein, reported a case of imipenem-cilastatin-induced seizure in a 20-year-old patient.

***Case Presentation*:** A 20-year-old male was admitted to the intensive care unit for febrile status epilepticus and acute respiratory distress syndrome. Initial evaluations ruled out underlying causes and anti-epileptic treatment has been initiated. Despite having an effective anti-epileptic treatment for three months of hospitalization, seizure recurrence occurred, leading to antibiotic regimen adjustment as the imputability of imipenem-cilastatin was suspected. After discontinuation of the involved drug, the patient remained neurologically stable. Previous literature has reported cases of imipenem-cilastatin-induced seizures, particularly in elderly patients or at higher dosages. The causality assessment was conducted using the updated French method, which rated the chronological criterion as C2 and the semiological criterion as S2. The intrinsic imputability score was I3, indicating plausible causality, and the extrinsic bibliographic score was B3.

***Conclusion*:** Our case has highlighted the importance of promptly recognizing imipenem-cilastatin-induced epileptic seizures in order to treat them more effectively and thus optimize the patient's care. Therefore, we emphasize that clinicians be vigilant about the side effects of its use, particularly in patients with neurological susceptibilities. We also advocate a personalized choice of antibiotics, taking into account both antimicrobial efficacy and potential adverse effects, for better outcomes with fewer risks.

Keywords: Imipenem-cilastatin, seizure, side effects, drug monitoring, pharmacovigilance, case report.

1. INTRODUCTION

Imipenem-cilastatin, a carbapenem antibiotic, has a broad spectrum of antimicrobial activity, and it is commonly used to treat severe bacterial infections. The importance of its use has increased due to the alarming rise in antibiotic resistance, particularly among hospitalized patients, as imipenem-cilastatin continues to be effective in treating a variety of infections caused by resistant Gram-negative bacteria [1].

We have, herein, reported an encountered case, wherein seizures induced by imipenem-cilastatin in a 20-year-old patient have prompted the discontinuation of this antibiotic and the switch in the treatment. The patient remained neurologically stable thereafter without needing a change in the anti-epileptic treatment regimen.

2. CASE PRESENTATION

A 20-year-old male patient was admitted to the Intensive Care Unit (ICU) of our hospital in November 2021, presenting a febrile status epilepticus and Acute Respiratory Distress Syndrome (ARDS). At admission, profuse white secretions were present, and the heart rate was 140 beats/min. Glascow's score was 9/15 with spontaneous opening of the eyes and withdrawal to painful stimulation. The patient had no significant medical history.

Initial evaluations, including a cerebral scan and lumbar puncture, were conducted to assess neurological status and rule out potential underlying causes of the febrile status epilepticus. The result of the lumbar puncture showed a rock water-like fluid with the presence of 3 leukocytes and 900 red blood cells without hypoglycorrhachia or hyperproteinorrhachia. The cerebral scan showed no abnormalities. In addition, virology tests were carried out on the cerebrospinal fluid, including tests for CMV, EBV, HSV, and COVID-19. Other tests were performed on blood for West Nile virus, Toscana virus, EBV, hepatitis B and C, and HIV. All the mentioned tests were negative. Further, brain MRI showed no signs of meningoencephalitis. The patient was intubated given the important need for oxygen and extracorporeal membrane oxygenation was performed. The evolution was marked by improvement in the oxygenation ratio and the patient was subsequently tracheostomized.

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To manage seizures, anti-epileptic treatment was prescribed. The patient received phenytoin and levetiracetam. Neurological stability was achieved with a treatment regimen consisting of 100 mg phenytoin three times a day and 1.5 g levetiracetam twice a day. In addition to that, a continuous infusion of valproic acid was prescribed if needed.

The patient initially received empiric treatment, including injectable 10 mg/kg acyclovir three times a day and 2 g cefotaxime three times a day. Bacteriological tests were negative, but due to persistent fever, vasoplegia, and high inflammatory markers levels (CRP 68 mg/ml), treatment was adjusted on December 7th. Amikacin was started at 30 mg/kg per day for 5 days, along with piperacillin/tazobactam at 4 g/500 mg four times a day and vancomycin at 15 mg/kg twice a day for 7 days. On December 15th, the patient presented hemodynamic instability, hypoxia, and changes in bronchial secretions, accompanied by increased Procalcitonin (PCT) level to 22 µg/L and CRP to 168 mg/ml. Colistin and linezolid were initiated intravenously. Three days later, antibiotic therapy was adjusted based on positive blood cultures for *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, with meropenem at 2 g three times a day for 9 days and amikacin at 30 mg/kg per day for 5 days. The patient became afebrile with PCT decreasing to 0.35 g/L and CRP to 104 mg/ml. The patient remained stable for two weeks with consistent CRP and PCT levels and good respiratory function under ventilation.

In January, the patient presented a new febrile episode (a 39°C-plateau) and a notable elevation in CRP level (159 mg/L). The diagnosis of bacteremic pneumonia was confirmed with a positive hemoculture, which *Klebsiella pneumoniae* was responsible for. To manage the infection, the treatment included inhaled colistin at a dosage of 4,5 MUI twice a day (completed at 7 days), amikacin 30 mg/kg per day (completed at 4 days), and imipenem-cilastatin 500 mg/500 mg at a dosage of 1 g/1 g three times a day initially, and then ciprofloxacin intravenously was added the next day at a dosage of 400 mg three times a day (completed at 14 days).

Despite good clinical outcomes, the inflammatory syndrome persisted. Therefore, 1g imipenem-cilastatin three times a day has been extended due to concerns about the potential persistence of the infection.

Throughout the period of hospitalization, the patient did not present any other significant seizures. However, he experienced a recurrence of seizures on February 8th. The patient's renal function was correct and data regarding medication plasma levels were not available at that time.

A conversation between pharmacists and clinicians was conducted to deal with the treatment in cause. The patient was treated only with imipenem-cilastatin for 28 days and with anti-epileptic drugs when the seizures occurred. This led to incriminating imipenem-cilastatin as the probable cause of the seizures and to a switch in antibiotic therapy to meropenem 2 g three times a day, ertapenem 1 g per day, and amikacin 30 mg/kg per day. This switch was prompted by concerns over neurological side effects, specifically seizures associated with imipenem-cilastatin. Imipenem-cilastatin was replaced with meropenem, which offered a similar spectrum of activity, but with potentially lower neurotoxicity risks. Ertapenem was specifically chosen to complement the treatment regimen because of its ability to saturate carbapenemases, so it helped maintain an effective concentration of meropenem in the body, thereby enhancing the overall treatment's ability to eliminate bacteria. This synergistic combination has been found crucial for overcoming the resistance mechanisms of pathogens. Amikacin was retained for its effectiveness against multidrug-resistant Gram-negative bacteria, enhancing coverage with carbapenems. So, the clinical decisions were guided by monitoring inflammatory markers and symptoms to ensure effective management of *Klebsiella pneumoniae* bacteremic pneumonia, leading to neurological stabilization after discontinuation of imipenem-cilastatin.

Clonazepam was initiated later due to spasticity. Subsequently, the patient remained stable with no recurrence of seizures under a regimen of 1.5 g levetiracetam twice daily and 2 mg clonazepam daily.

3. DISCUSSION

In our case, the patient remained on imipenem-cilastatin for 28 days in order to treat his bacteremic pneumonia. After the recurrence of seizures, we recommended switching the patient's antibiotic treatment given the suspicion that the involved antibiotic might have induced the seizures.

Imipenem-cilastatin-induced seizures have been reported in the literature [1-6]. In some cases, an overdose has been reported to be responsible for neurological toxicity [3]. Basil *et al*. [3] published the case of a 67-year-old woman with chronic renal failure and creatinine clearance of 10–20 mL/min, who developed seizures during treatment with imipenem for community-acquired pneumonia and suspected melioidosis. The patient was treated with IV imipenem 500 mg every 12 hours. The authors noted that the antibiotic was administered at doses exceeding recommendations for her renal function as the dose should have been 250 mg every 12 hours. In our case, the patient's renal function was preserved, and the dose of imipenem-cilastatin was adequate (1 g every 8 hours).

Additional studies have shown interest in elderly patients who may be particularly vulnerable to this side effect [4, 5]. Nielly *et al*. [4] found that the combination of too high a dose of imipenem-cilastatin and impaired kidney function led to the accumulation of imipenem in the brain tissue, which caused the seizures. In our case, the patient was younger, and the prolonged duration of the prescription possibly led to the accumulation of the drug in the central nervous system.

In another published case by Zhao *et al*. [5], a 78-year-old man developed an epileptic seizure during treatment with imipenem-cilastatin for a pulmonary infection after an unsuccessful treatment with ceftizoxime. Three days into re-

ceiving imipenem-cilastatin 500 mg/500 mg every 8 hours, he experienced a seizure, which was managed with oxygen, diazepam, and phenobarbital sodium, leading to his subsequent recovery and discharge. In this case, the seizure occurred much earlier than in our case, and the authors did not mention the patient's renal function.

Regular assessment of renal function is crucial in patients receiving imipenem to adjust dosages based on creatinine clearance levels. Besides, monitoring drug plasma levels helps prevent toxicity by ensuring that imipenem concentrations remain within the therapeutic range for optimal antibacterial effects. Since imipenem is a time-dependent antibiotic, its antibacterial effectiveness relies on the duration that free drug concentrations remain above the minimum inhibitory concentration (f%T>MIC) within the dosing interval.

This close monitoring allows for timely dose adjustments to avoid drug accumulation and potential adverse effects [7]. Unfortunately, measuring imipenem plasma levels was not possible, as Therapeutic Drug Monitoring (TDM) of beta-lactams has not yet been implemented in Tunisia.

Structurally akin to the penicillin class, carbapenems are typically well-tolerated by most patients. Nevertheless, a significant side effect has been associated with their administration, which is Central Nervous System (CNS) toxicity [8]. In this context, a study has shown that carbapenem antibiotics, including imipenem-cilastatin, have a similar structure to the Gamma-aminobutyric Acid (GABA) receptors, which leads to seizure activity by inhibiting those receptors [9]. In fact, the GABA as a neurotransmitter facilitates inhibitory neurotransmission by activating the GABA-A receptor complex. This receptor operates as a ligand-gated chloride ion channel made up of various subunits, with the benzodiazepine, barbiturate, and GABA binding sites being the most clinically significant [10]. When GABA binds to its receptor site, it opens the chloride channel, allowing chloride ions to flow into the postsynaptic nerve terminal. This ion flow causes hyperpolarization of the membrane potential, which decreases the cells' excitability [11]. Conversely, antagonism of GABA binding by imipenem-cilastatin leads to an increased membrane potential, creating an excitatory state that is more prone to depolarizing in response to stimuli.

Besides GABA inhibition, another mechanism involves the agonism of excitatory glutamatergic N-methyl-D-aspartate (NMDA) receptors [12].

It is also recognized that cilastatin does not play a role in this epileptogenic potential [13]. Early clinical investigations have revealed a correlation between the use of imipenem and the onset of seizures, a concern that persists with the use of carbapenems, particularly at higher dosages [9, 14].

In our case, the discontinuation of imipenem-cilastatin, which led to the cessation of seizures, suggested its potential involvement in their recurrence. The reported cases in the literature have consistently yielded identical outcomes [2, 4, 5].

The updated French method causality assessment of imipenem-cilastatin-induced seizures in this patient has indicated a plausible causal relationship between the drug and seizure recurrence. This methodology evaluates three primary criteria: chronological, semiological, and bibliographic. Chronologically, a clear temporal association exists between imipenem-cilastatin administration and seizure onset, likely due to drug accumulation, with improvement following discontinuation, warranting a C2 rating. Semiologically, seizures are a well-documented adverse effect of imipenem--cilastatin, evocative of the role of this drug, justifying an S2 rating. Bibliographically, substantial literature evidence supports this link, resulting in a B3 rating. The final intrinsic imputability score was I3 (on a scale from I0 to I6), derived from combining C2 and S2 scores, indicating plausible causality. This assessment has been further corroborated by the extrinsic bibliographic score of B3, collectively providing strong evidence for a causal relationship between imipenem-cilastatin and the observed seizures in this patient.

There is a widely held agreement among clinicians that imipenem-cilastatin stands out as the most epileptogenic among the carbapenems. However, some authors suggest otherwise [1]. Cannon *et al*. [1] conducted a meta-analysis revealing that imipenem demonstrated a higher epileptogenic potential compared to non-carbapenem antibiotics. Conversely, meropenem, ertapenem, and doripenem were not found to be associated with an elevated risk of seizures.

CONCLUSION

The onset of recurrent seizures in our patient, despite effective antiepileptic treatment, raised suspicion regarding imipenem-cilastatin as a potential cause. This suspicion was confirmed by the resolution of seizures upon stopping imipenem-cilastatin and the absence of their recurrence with alternative antibiotic therapy and the same antiepileptic treatment.

We emphasize the importance of identifying imipenem--cilastatin-induced seizures and taking prompt action to ensure patient safety. We also intend to implement TDM of imipenem-cilastatin in our hospital setting. Furthermore, we plan to conduct research to evaluate the effectiveness of TDM in preventing neurological complications. This initiative can enhance patient safety and optimize therapeutic outcomes.

Moreover, our case has highlighted the need for personalized antibiotic selection considering both antimicrobial efficacy and potential side effects to optimize patient outcomes while minimizing the risks.

AUTHORS' CONTRIBUTION

MAY contributed to the study conception and design; GA and BBH drafted the manuscript. All authors have reviewed the results and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Informed consent was obtained from the patient.

STANDARD OF REPORTING

CARE guidelines were followed.

AVAILABILITY OF DATA AND MATERIAL

All data generated or analysed during this study are included in this published article.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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