

## Cefoperazone-Sulbactam Induced Focal Seizures in Acute Myeloid Leukemia: A Case Report

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### Abstract: -

Cefoperazone-sulbactam is a broad-spectrum antibiotic combination of  $\beta$ -lactam and  $\beta$ -lactamase inhibitors that is commonly used in treatment of severe bacterial infections and febrile neutropenia. While cephalosporin-induced neurotoxicity is known, seizures are rarely seen in patients treated with cefoperazone-sulbactam, especially those who do not have severe renal impairment.

Case Presentation: - A 59-year-old female with a history of Acute Myeloid Leukemia (AML) being treated with high-dose cytarabine chemotherapy (HDC) had a history of fever, chills, generalized weakness and was suspected to have febrile neutropenia (FN). Intravenous cefoperazone-sulbactam (3 g) was started empirically. Immediately after infusion, the patient experienced focal seizures involving the right upper limb and these quickly progressed to generalized tonic-clonic seizures (GTCS) with postictal confusion. The patient was immediately withdrawn from cefoperazone-sulbactam, and treated with intravenous levetiracetam, supportive measures and neurologic monitoring, with complete recovery without recurrence.

This is a rare case of cefoperazone-sulbactam mediated neurotoxicity which presented as focal seizures that progressed to GTCS in an AML patient without renal dysfunction. The key points in early recognition, prompt removal of offending agent and timely supportive management are essential to avoid serious neurological complications.

### I. Introduction: -

Cefoperazone is the third generation of cephalosporin antibiotics with a wide antibacterial spectrum and strong effect. However, cefoperazone is highly susceptible to the hydrolysis by plasmid- and chromosome-mediated  $\beta$ -lactamases, resulting in the decline in the curative effect. Sulbactam is a  $\beta$ -

lactamase inhibitor, which has an irreversible inhibitory effect on  $\beta$ -lactam antibiotic resistant strains<sup>[1]</sup>. Cefoperazone: Sulbactam ratio (2:1) would constitute a combination form of cefoperazone/sulbactam, which has better activities against *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* than cefoperazone alone<sup>[2]</sup>

In recent years, cefoperazone-sulbactam, a broad-spectrum antibiotic, has been widely used to treat various acute bacterial infections. Notably, cefoperazone-sulbactam has demonstrated strong in vitro antibacterial activity against ESBL-producing *Enterobacteriaceae* and carbapenem-resistant *Acinetobacter baumannii*, without being affected by the inoculum effect.<sup>[3]</sup> This combination is commonly used in respiratory tract infections, urinary tract infections, intra-abdominal infections, septicemia, febrile neutropenia, and nosocomial infections etc. Also, this combination can be used in immunocompromised patients, and disease susceptible patients.<sup>[4]</sup> Due to its broad-spectrum efficacy, this drug combination is extensively prescribed in tertiary care hospitals, intensive care units, and oncology departments for infection prone patients.<sup>[1,3]</sup>

Despite strong therapeutic benefits, cephalosporin class also possess neurotoxicity especially in widely used combination like cefoperazone-sulbactam which may possess an increasingly recognized adverse effects.<sup>[5]</sup> Neurological complications include encephalopathy, confusion, agitation, hallucinations, aphasia, myoclonus, focal neurological deficits, and seizures etc.<sup>[6]</sup>

The pathophysiology of cefoperazone-sulbactam combinedly primarily involve competitive inhibition of gamma-aminobutyric acid (GABA)-A receptors which are ligand gated ion channel receptors and primary inhibitory neurotransmitter receptor in CNS responsible for reducing neuronal excitability

producing a calming, sedative and anticonvulsant effect within the central nervous system, resulting in neuronal hyperexcitability and seizure activity .<sup>[6,7]</sup> Several risk factors for predispose patients to  $\beta$ -lactamase induced neurotoxicity including advanced age, renal impairment, underlying neurological disorders, electrolyte imbalance, sepsis, malignancy, and high-dose antibiotic therapy<sup>[8]</sup>.

**Acute myeloid leukemia (AML)** starts in the bone marrow, the soft inner part of certain bones, where new blood cells are made. Most often AML quickly moves from the bone marrow into the blood. It can sometimes spread to other parts of the body including the lymph nodes, liver, spleen, central nervous system (brain and spinal cord), and testicles. Sometimes leukemia cells form a tumor called a myeloid sarcoma. Patients with hematological malignancies such as Acute Myeloid Leukemia (AML) are particularly vulnerable because of altered blood-brain barrier permeability, immunosuppression, metabolic disturbances, systemic inflammation, and concurrent exposure to multiple potentially neurotoxic agents<sup>[9,10]</sup>. Although cefepime and other cephalosporin induced neurotoxicity are well documented, but cefoperazone-sulbactam combination induced seizures and other neurotoxic effects are uncommon.<sup>[11]</sup> Early identification of such adverse reactions is clinically important because neurological deterioration in oncology patients may mimic infectious, metabolic, or malignant etiologies<sup>[12]</sup>. Therefore, we present a case present a rare case report of observed neurotoxic Adverse Drug Reaction (ADR) of Cefoperazone-Sulbactam Induced Focal Seizure progressing to Generalized Tonic Clonic Seizure (GTCS) in Acute Myeloid Leukemia patient.

## II. Case Summary: -

A 59 year old female patient, approximately weighing 61 Kg, presented to emergency department of the Hospital with complaints of fever with chills, generalized weakness and body ache for 3–4 days. The patient had previously been diagnosed with Acute Myeloid Leukemia (AML) in December 2025 and had received three courses of high dose cytarabine chemotherapy (HiDAC protocol). At the time of admission, the patient was alert and oriented. Vital signs were as follows: temperature 101°F, pulse rate 100 beats per minute, respiratory rate 20 breaths per minute, blood pressure 146/90 mmHg and oxygen saturation 97% on room air. On physical

examination, there were no focal neurological deficits, and was pallor with generalized weakness. Laboratory examination revealed a hemoglobin of 10.6 g/dL, a total leukocyte count of 5,120 cells/mm<sup>3</sup>, a platelet count of 75,000 cells/mm<sup>3</sup>, a serum creatinine of 0.9 mg/dL, a blood urea nitrogen of 18 mg/dL, a sodium level of 138 mEq/L, a potassium level of 4.1 mEq/L, an SGOT of 32 IU/L, a SGPT of 30 IU/L, and a serum bilirubin of 0.8 mg/dL. There were no abnormalities in renal and hepatic function tests. Empirical treatment with Cefoperazone-Sulbactam (Inj. Zostum) 3 g infusion was started immediately following the appearance of febrile neutropenia and a suspect of bacterial infection in the immunocompromised patient. The patient became agitated and started to develop focal seizures in the right upper limb within minutes of the infusion that quickly deteriorated to generalized tonic-clonic seizure (GTCS). The duration of the episode was about 2-3 minutes with postictal confusion. No history of previous epilepsy, seizure disorder, cerebrovascular accident or central nervous system pathology. Immediately stopped the infusion of cefoperazone-sulbactam. Levetiracetam given intravenously as a single dose of 1 g, oxygen supplementation, intravenous fluids and close neurological monitoring were used to treat the patient. Immediate referral to neurology was undertaken. A computed tomography (CT) scan of the brain showed no acute intracranial disease. There were no values of serum electrolytes or metabolic parameters that were abnormal, which ruled out metabolic causes of seizures. During hospitalization, the patient gradually recovered her neurological function without further seizure attacks and was not administered any further treatment with cefoperazone-sulbactam. Since the patient's status was immunocompromised and she was suspected of having a bacterial infection, alternative antimicrobial treatment was started with intravenous Meropenem. During hospitalization, patient remained hemodynamically stable and was discharged with symptomatic improvement and advice for oncological follow up.

The score on Naranjo Adverse Drug Reaction Probability Scale was 7 which means that there was a “Probable” adverse drug reaction<sup>[7]</sup>.

For this reaction, the WHO-UMC causality assessment criteria was used, and the reaction was rated as “Probable/Likely”<sup>[8]</sup>.

Sr.No.: -	Naranjo Questionnaire	Response	Score
1	Are there previous conclusive reports on this reaction?	Yes — cephalosporin-induced neurotoxicity and seizures have been previously reported.	+1
2	Did the adverse event appear after the suspected drug was administered?	Yes — seizures developed within minutes after initiation of cefoperazone-sulbactam infusion.	+2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	Yes — seizures subsided after discontinuation of cefoperazone-sulbactam and supportive treatment.	+1
4	Did the adverse reaction reappear upon re-administration of the drug?	Not performed	0
5	Are there alternative causes that could solely have caused the reaction?	No — CT brain, electrolytes, renal and hepatic parameters were normal; no prior seizure history.	+2
6	Did the reaction reappear when a placebo was given?	Not applicable.	0
7	Was the drug detected in toxic concentrations in blood or other fluids?	Not performed.	0
8	Was the reaction more severe with increased dose or less severe with decreased dose?	Not assessed.	0
9	Did the patient have a similar reaction to the same or similar drugs in previous exposure?	No.	0
10	Was the adverse event confirmed by any objective evidence?	Yes — focal seizure progressing to GTCS was clinically observed and documented by treating physicians.	+1
			TOTAL: - 7

Table-1 Naranjo Adverse Reaction Probability Scale

Category	Criteria
Certain	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality with plausible time relationship to drug intake</li> <li>• Cannot be explained by disease or other drugs</li> <li>• Response to withdrawal plausible pharmacologically or pathologically</li> <li>• Event definitive pharmacologically or phenomenologically (i.e., objective and specific medical disorder or a recognized pharmacologic phenomenon)</li> <li>• Rechallenge satisfactory, if necessary</li> </ul>
Probable / Likely	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality with reasonable time relationship to drug intake</li> <li>• Unlikely to be attributed to disease or other drugs</li> <li>• Response to withdrawal clinically reasonable</li> <li>• Rechallenge not required</li> </ul>
Possible	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality with reasonable time relationship to drug intake</li> <li>• Could also be explained by disease or other drugs</li> </ul>

	<ul style="list-style-type: none"> <li>• Information on drug withdrawal may be lacking or unclear</li> </ul>
Unlikely	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality with a time to drug intake that makes a relationship improbable (but not impossible)</li> <li>• Disease or other drugs provide plausible explanations</li> </ul>
Conditional / Unclassified	<ul style="list-style-type: none"> <li>• Event or laboratory test abnormality</li> <li>• More data for proper assessment needed, or additional data under examination</li> </ul>
Unassessable / Unclassifiable	<ul style="list-style-type: none"> <li>• Report suggesting an adverse reaction</li> <li>• Cannot be judged because information is insufficient or contradictory</li> <li>• Data cannot be supplemented or verified</li> </ul>

Table -2 UMC Causality Assessment Scale

### III. Discussion: -

Cephalosporin induced neurotoxicity, adverse reactions and adverse events are not very common but are serious reactions which needs medical attention in hospitalized and critically ill patients.<sup>[13]</sup> Amongst Beta lactamase inhibitors cefepime has more frequent neurotoxic adverse events, however recent literature suggests that other antibiotics of same class like cefoperazone-sulbactam also possess serious neurotoxicological adverse reaction.<sup>[14,19]</sup> Neurological adverse reactions associated with cephalosporin class antibiotics include agitation, hallucinations, aphasia, confusion, encephalopathy, focal neurological deficit, generalized tonic clonic seizures, status epilepticus etc. Adverse Reaction may start to appear immediately after initiation of the therapy and may resolve by its own after withdrawal of the offending drug.<sup>[15,16]</sup> The exact mechanism of cephalosporin class antibiotics induced seizures are not completely understood but inhibition of GABA-A receptors within the central nervous system(CNS) is considered as primary mechanism responsible for neuronal hyperexcitability leading to adverse drug reaction.<sup>[6,7]</sup> B-Lactamase antibiotics may completely antagonize the inhibitory neurotransmitters facilitating epileptogenic activity. In addition to this, systemic inflammation, blood-brain barrier dysfunction, renal insufficiency, electrolyte imbalance, and elevated serum antibiotic concentrations etc. may further contribute to neurotoxicity.<sup>[17,18]</sup>

Oncology patients are especially susceptible because of altered pharmacokinetics, prior chemotherapy exposures, immunocompromised functionality, metabolic disturbances, frequent use of multiple medications (polytherapy) etc. Acute Myeloid

Leukemia (AML) itself is associated with several neurological complications including leukemic infiltration, cerebrovascular events, opportunistic infections, metabolic encephalopathy, and chemotherapy-related neurotoxicity.<sup>[20,21]</sup> Consequently, neurological symptoms occurring in AML patients often present with diagnostic challenges. Drug-induced neurotoxicity may be overlooked or misdiagnosed as disease progression or metabolic complications which is a serious matter for attention.<sup>[22]</sup>

In the present case the patient as soon as the infusion of Cefoperazone-Sulbactam started the patient developed focal seizures progressing to generalized tonic-clonic seizures (GTCS) within minutes showcasing a strong association between them. Alternative etiologies including electrolyte abnormalities, intracranial pathology, prior seizure disorder, and metabolic disturbances were excluded through clinical and laboratory evaluation. Interestingly, our patient demonstrated near-normal renal function. Renal dysfunction is considered one of the most important predisposing factors for cephalosporin-induced neurotoxicity because impaired renal clearance results in elevated serum and cerebrospinal fluid concentrations<sup>[23]</sup> However there are several literature reports suggesting that cephalosporin antibiotics may induce seizure and other neurotoxic effects even without any renal impairment particularly among geriatric and critically ill patients.<sup>[24]</sup> A systematic review by Sutter et al. reported that antibiotic-associated seizures are increasingly encountered with  $\beta$ -lactam antibiotics and are frequently underrecognized in clinical practice<sup>[7]</sup>. Similarly, Appa et al. highlighted that neurotoxicity associated with cephalosporins

may present acutely and mimic metabolic or infectious encephalopathy<sup>[13]</sup>

Management of such reaction involves immediate withdrawal of offending drug, seizure control with antiepileptic therapy, supportive care and correction of metabolic abnormalities. <sup>[25]</sup> In our patient, immediate discontinuation of cefoperazone - sulbactam infusion and rapid administration of intravenous Levetiracetam resulted in complete neurological recovery without any recurrence of seizures. This emphasizes the importance of early identification of Adverse Drug Reactions and immediate correction of it. This case also emphasizes on Importance of Pharmacovigilance in Oncology and critically ill patients. ADR reporting remains essential for identifying rare and potentially serious adverse effects associated with commonly prescribed medications. Active monitoring of neurological symptoms during  $\beta$ -lactam therapy may improve patient safety and reduce morbidity among immunocompromised patients.

#### IV. Conclusion: -

Cefoperazone-sulbactam is broad-spectrum antibiotic combination widely used in the treatment of severe bacterial infections and febrile neutropenia. In this case, however, cefoperazone-sulbactam has observed to cause serious neurological reaction such as focal seizures and generalized tonic-clonic seizures, even in the absence of significant renal dysfunction. Patients with AML and other hematological malignancies may have higher risk due to immunocompromised status, chemotherapy treatment and altered physiologic state of body. The key to obtaining good clinical results is early recognition of the drug-induced neurotoxic effect, withdrawal of the toxic agent and supportive therapy. Careful neurological monitoring and active pharmacovigilance is crucial during  $\beta$ -lactam antibiotic treatment of oncology patients.

This case deeply demonstrates the importance of careful and detailed neurological monitoring and active pharmacovigilance during cefoperazone-sulbactam combination antibiotic therapy in Oncology patients.

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