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CASE REPORT

Ceftazidime-Avibactam-Induced Neurotoxicity Manifesting as Seizure in an Older Adult: A Case Report

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Abstract: This single-case report describes severe neurotoxicity manifesting as seizure in an older, critically ill patient with acute kidney injury during treatment with ceftazidime-avibactam (CZA-AVI), a combination antibiotic used for multidrug-resistant Gram-negative infections. Although generally safe, neurotoxicity from CZA-AVI, while uncommon, can be severe. The patient, a 78-year-old woman with multiple comorbidities and acute kidney injury, developed impaired consciousness progressing to generalized seizures a few days after initiating CZA-AVI. Electroencephalography confirmed seizure activity. All other potential causes were excluded. Her neurological symptoms resolved completely after discontinuation of CZA-AVI and initiation of antiepileptic therapy. This case highlights that CZA-AVI carries a risk of serious neurotoxicity, particularly in vulnerable populations such as older, critically ill patients with renal impairment. It underscores the imperative for strict adherence to renal dose adjustment guidelines, vigilant neurological monitoring, and immediate consideration of drug-induced encephalopathy in the differential diagnosis of mental status changes in such patients. Awareness of this potential adverse event should be integrated into antimicrobial stewardship programs to optimize patient safety.

Keywords: adverse reaction, ceftazidime avibactam sodium, neurotoxicity, risk factors, seizure, therapeutic drug monitoring

Introduction

Ceftazidime avibactam (CZA-AVI) is a novel beta-lactam and beta-lactamase inhibitor combination used to treat Gram-negative bacillary infections. It contains a fixed-dose formulation of ceftazidime, a third-generation cephalosporin, and avibactam, a non-beta-lactam beta-lactamase inhibitor. CZA-AVI received approval from the United States Food and Drug Administration in February 2015 and was authorized for clinical use in China in May 2019. It is indicated for treating complicated intra-abdominal infections, hospital-acquired pneumonia including ventilator-associated pneumonia, and complicated urinary tract infections caused by multidrug-resistant or extensively drug-resistant Gram-negative bacteria.[1–4] CZA-AVI has demonstrated favorable efficacy and a good safety profile in infections caused by Gram-negative bacilli, particularly carbapenem-resistant Enterobacterales and Pseudomonas aeruginosa, and has therefore been widely used in clinical settings. Reported adverse effects commonly include gastrointestinal disturbances, headache, dizziness, and elevated transaminases, while severe adverse events remain uncommon.[5] Severe neurological manifestations following CZA-AVI administration have been reported infrequently. In a study by Guo et al,[6] a total of 832 cases of adverse events (AEs) related to CAZ-AVI were reported, among which 130 cases were related to the central nervous system (CNS). Notably, the majority of the reported cases were female (48.46%), and the proportion of elderly patients (aged 65 years or older) was higher than that in other age groups. This report describes a novel and instructive case of CZA-AVI-induced neurotoxicity manifesting as seizure in an older, critically ill patient with acute kidney injury,

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highlighting the challenges in dosing adjustment during renal function fluctuation and the severity of neurotoxicity that can occur. We summarize the relevant literature to underscore the importance of vigilance and informed decision-making to support the rational and safe clinical use of this antimicrobial agent in high-risk populations.

Case Analysis

The patient, a 78-year-old woman (height 160 cm, weight 75 kg), presented to Beijing Electric Power Hospital on Day-3 (3 days prior to the initiation of CZA-AVI) with a 20-day history of fever, dyspnea, edema, and oliguria. Her medical history included rheumatic heart disease for several decades, for which she underwent mitral valve replacement with a mechanical prosthesis in 2003, followed by long-term warfarin anticoagulation therapy. The patient had longstanding hypertension that remained well controlled with antihypertensive therapy, as well as coronary artery disease with prior coronary stent implantation and chronic heart failure for several years, both managed with antiplatelet therapy and statins (specific regimens unknown). The patient also had type 2 diabetes mellitus with good glycemic control on regular medication. She denied any history of psychiatric disorders or cerebrovascular events.

Twenty days before admission, the patient developed fever, dyspnea, edema, and oliguria and was hospitalized at another hospital. After evaluation, the patient was diagnosed with pulmonary infection, urinary tract infection, acute decompensated heart failure, and acute kidney injury. The patient received moxifloxacin along with inotropic therapy and diuretics, after which her symptoms improved and she was discharged. Five days before the current admission, similar symptoms recurred, including chest tightness, dyspnea, and fever of approximately 38°C, accompanied by urine output decreasing to less than 100 mL over 3 days and marked bilateral lower-extremity edema. The patient was readmitted to another hospital and treated with moxifloxacin, inotropic agents, and diuretics, but her condition progressively worsened and was accompanied by intermittent cough with sputum production. The patient was subsequently transferred to Beijing Electric Power Hospital for further management and was admitted to the intensive care unit due to the severity of her condition.

At admission, the patient reported chest tightness and dyspnea. The patient was conscious but appeared to be in poor general condition, with a respiratory rate of 25 breaths per minute, oxygen saturation of 96% (FiO2 35%), heart rate of 92 beats per minute, blood pressure of 146 over 63 mmHg, and temperature of 36.2°C. Auscultation demonstrated extensive moist rales bilaterally, diminished breath sounds in the right lower lung field, slightly muffled heart sounds, and marked edema of all extremities.

Auxiliary examinations: Bedside chest radiography revealed multiple pulmonary infiltrates, bronchial changes in both lungs, a small right pleural effusion, and findings consistent with cardiac pacemaker placement. Cardiac markers demonstrated an NT proBNP level of 12,100 pg/mL, with normal troponin and creatine kinase MB levels. Inflammatory markers included procalcitonin (PCT) 0.46 ng/mL, C-reactive protein 63.18 mg/L, and interleukin 6 at 35.3 pg/mL. Additional laboratory data demonstrated serum creatinine 215 μmol/L, albumin 33.0 g/L, hemoglobin 90.0 g/L, negative urinary ketones, normal electrolytes, and normal transaminases, bilirubin, amylase, and lipase.

Initial admission diagnosis: Multiple organ dysfunction syndrome; acute decompensated heart failure (NYHA class IV); acute kidney injury; pulmonary infection; urinary tract infection; hypoalbuminemia; mild anemia; coronary atherosclerotic heart disease; rheumatic heart disease; status post-mechanical mitral valve replacement; status post-coronary stent implantation; status post-cardiac pacemaker implantation; grade 3 hypertension (very high risk); type 2 diabetes mellitus.

Following admission, the patient received oxygen via face mask and was treated with isosorbide dinitrate for coronary vasodilation, deslanoside for inotropic support, and ilaprazole for stress ulcer prophylaxis. The co-medication is presented in Supplementary Material. The continuous renal replacement therapy (CRRT) mode was continuous veno-venous hemofiltration (CVVH), which was used to achieve negative fluid balance and reduce serum creatinine levels. The anticoagulation method was regional citrate anticoagulation. The parameter settings were as follows: blood flow rate (BFR) = 150mL/min, replacement fluid flow rate = pre-dilution 1500mL/h + post-dilution 1000mL/h, and negative fluid volume per hour = 200mL. Given the severity of pneumonia, recent hospitalization, and purulent sputum, infection with multidrug-resistant Gram-negative bacilli, predominantly Enterobacterales, was considered most likely, although Gram-positive cocci could not be excluded. In the context of her prior mechanical mitral valve replacement and the need for

timely infection control, empirical antimicrobial therapy with meropenem (1 g every 8 hours during hemofiltration, loading dose of 2 g) combined with teicoplanin (0.4 g every 12 hours on day 1) was administered to provide coverage against both Gram-negative and Gram-positive organisms. Microbiological cultures were obtained. Within 3 hours of initiating therapy, the patient's symptoms improved and urine output increased to 100 mL per hour.

On Day-2, the patient was alert with a Glasgow Coma Scale (GCS) score of 15, stable respirations, and a maximum temperature of 37.5°C. The patient reported mild dyspnea, and lower extremity edema had decreased, but urine output gradually declined. The treatment regimen was continued (antibiotic dosing during hemofiltration: meropenem 1 g every 8 hours; teicoplanin 0.4 g daily). As urine output decreased to 20 mL per hour, hemofiltration was discontinued following completion of the antibiotic infusion.

On Day-1, the patient remained alert with stable respirations and further reduction in lower extremity edema. The maximum temperature was 37.8°C, high-sensitivity CRP was 87.51 mg/L, and NT proBNP was 8170 pg/mL. Following intermittent diuretic administration, urine output increased to approximately 40 mL per hour. Given the low likelihood of resistant Gram-positive infection; the broad activity of meropenem against most Gram-negative bacilli and some Gram-positive cocci; and the patient's stable respiratory and hemodynamic status, teicoplanin was discontinued. Meropenem was continued at 0.5 g daily (adjusted for the low urine output observed on the previous day) for ongoing antimicrobial therapy.

On Day 1 (refers to the first day of CZA-AVI administration), the patient (estimated weight 70kg) remained alert with stable hemodynamics. Bedside echocardiography indicated improved cardiac function. Throat swab culture yielded carbapenem-resistant *Klebsiella pneumoniae* (CRKP). Serum creatinine was 149 μmol/L, and morning urine output ranged from 20 to 60 mL per hour. Recent guidelines, including the Infectious Diseases Society of America guidelines for Gram-negative infections and the Chinese Guidelines for the Clinical Application of Antibacterial Drugs in Febrile Neutropenia (2020 edition),[7,8] recommend CZA AVI as first-line therapy for carbapenemase-producing Enterobacteriaceae and difficult-to-treat *P. aeruginosa*. The Chinese Expert Consensus on the Diagnosis, Treatment and Prevention of Infections Caused by Carbapenem resistant Enterobacteriaceae (CRE) notes that CZA-AVI achieves epithelial lining fluid concentrations exceeding 30% of plasma levels, supporting its use in CRE pneumonia.[9] The patient remained febrile, indicating incomplete infection control. Her creatinine clearance (CrCl), calculated using the Cockcroft Gault formula, was approximately 31 mL per minute. Given her limited urine output, the antimicrobial regimen was changed to ceftazidime–avibactam sodium 1.25 g every 12 hours. Coronary vasodilators and diuretics were continued. Following this adjustment, urine output increased to 100 mL per hour and the maximum temperature decreased to 37.3°C.

On Day 2, both pupils were equal, round, and reactive to light. Vital signs remained stable, and urine output exceeded 100 mL per hour. Laboratory tests demonstrated serum creatinine 156 μmol/L, CRP 35.39 mg/L, and PCT 0.28 ng/mL. That afternoon, the patient developed confusion with a GCS score of 10. Close monitoring was initiated while continuing the existing treatment plan.

On Day 3, total urine output from the previous day exceeded 3500 mL, and CRP decreased to 23.88 mg/L. The patient exhibited worsening mental status. Cranial computed tomography revealed multiple chronic ischemic foci, leukoaraiosis, encephalomalacia in the left occipital lobe and cerebellar hemisphere, and senile brain changes. A neurology consultation was obtained. Neurological examination demonstrated equal, round pupils (3 mm) with brisk light reflexes, symmetric facial features, and no pathological reflexes. The consultant recommended electroencephalography (EEG) to assess cerebral function and advised adding piracetam 0.8 g three times daily via nasogastric tube, continuation of current therapy for underlying conditions, and prevention of complications. Antimicrobial therapy remained effective. Although estimated CrCl on the previous day was 29 mL per minute, the marked increase in urine output indicated improving renal function. Considering the possibility of subtherapeutic dosing, CZA-AVI was increased to 2.5 g every 12 hours.

On Day 4, the patient became stuporous with a GCS score of 6, demonstrating intermittent convulsions and markedly increased muscle tone, consistent with atypical seizure activity. EEG revealed moderate abnormalities (Table 1). In the absence of prior neurological or psychiatric disease, no history of epilepsy, stable internal milieu, stable hemodynamics, and no evidence of acute infarction, hemorrhage, tumor, or cerebral edema on CT, the neurology team diagnosed

Table 1 Electroencephalography Findings During Acute Neurological Deterioration

Clinical diagnosis: Acute decompensated chronic heart failure	Medication/Other treatment: Diazepam	
Recording state: Stupor	Examination type: Routine EEG + video EEG	
Recording date: April 30, 2025	Recording duration: 40 minutes	Note: None
Background activity: 4 to 6 Hz θ rhythm, poor modulation/regulation, low-to-high amplitude, bilateral symmetry, eye opening/closure not completed		
Hyperventilation: Not performed		
Photic stimulation: No associated abnormalities observed		
Sphenoidal electrodes: Same as background		
Sleep cycle: Patient in stupor, sleep staging not performed		
Interictal discharges: Numerous low-to-high amplitude slow waves and sharp–slow waves with near-continuous discharge in all leads, predominantly on the left side		
Ictal events: The patient demonstrated numerous low-to-high amplitude slow waves and sharp–slow-wave complexes with near-continuous discharge across all leads. Diazepam 10 mg was administered by slow intravenous push as ordered. Approximately 3 minutes after administration, the frequency of sharp–slow-wave complexes decreased compared with baseline, and 5 minutes later, normal sleep rhythms gradually reappeared.		
EEG diagnosis: Moderate abnormal electroencephalogram		

probable drug-induced neurotoxicity with encephalopathy. CZA-AVI was strongly suspected as the causative agent for altered mental status and seizure activity. The medication was discontinued, and treatment was initiated with low-dose propofol for sedation, levetiracetam for seizure control, and Xingnaojing injection to promote awakening.

On Day 5, the patient remained unconscious with intermittent myoclonic jerks and reduced muscle tone (GCS 6). Inflammatory markers were mildly elevated with low-grade fever; no additional antibiotics were initiated.

On Day 6, the patient was somnolent with decreased limb twitching and normal muscle tone (GCS 8). The patient remained febrile (maximum temperature 38.5°C), with CRP 8.77 mg/L, PCT 0.35 ng/mL, and serum creatinine 180 μmol/L. Suspecting ongoing infection, combination therapy with meropenem (1 g every 12 hours, loading dose 2.0 g) and polymyxin B sulfate (750,000 units every 12 hours, loading dose 1,250,000 units based on body weight) was initiated.

On Day 7 and Day 8, the patient opened her eyes to verbal commands or painful stimuli but could not follow instructions. GCS remained 10 with intermittent low-grade fever. Current therapy was continued.

Over the following days, the patient's condition gradually improved. Mental status progressively recovered, seizures did not recur, infection was controlled, vital signs stabilized, and spontaneous voiding resumed.

On the morning of Day 9, the patient was alert, occasionally opened her eyes spontaneously, and was able to follow simple commands, with GCS 12. Temperature remained below 37.5°C, with CRP 3.99 mg/L, PCT 0.3 ng/mL, and serum creatinine 170 μmol/L.

On Day 10, repeat EEG (Table 2) demonstrated marked improvement compared with the previous study. GCS remained 12.

On Day 13, the patient was fully alert, followed commands, and opened her eyes spontaneously with GCS 15. Her overall condition had improved substantially, and her family elected to discharge her from the hospital.

A detailed timeline of the patient's clinical course, antimicrobial interventions, and neurological status changes is presented in Supplementary Table 1.

A Discussion of the Case Outcome

Association Between Seizure and Ceftazidime–Avibactam

After the patient developed altered mental status on Day 3, cranial CT was performed and neurology consultation was obtained. The neurologist recommended EEG. On Day 4, the patient became stuporous with intermittent convulsions indicative of seizure activity, prompting EEG that same day. EEG demonstrated loss of normal alpha waves, replaced by

Table 2 Follow-Up Electroencephalography Findings After Discontinuation of Ceftazidime-Avibactam

Clinical diagnosis: Acute decompensated chronic heart failure	Medication/Other treatment: None	
Recording state: Somnolent	Examination type: Routine EEG	
Recording date: May 6, 2025	Recording duration: 20 minutes	Note: None
Background activity: 5 to 7 Hz θ rhythm, suboptimal modulation/regulation, low-to-moderate amplitude, bilateral symmetry, eye opening/closure not completed		
Hyperventilation: Not performed		
Photic stimulation: No associated abnormalities observed		
Sphenoidal electrodes: Same as background		
Sleep cycle: Patient in somnolent state, sleep staging not performed		
Interictal discharges: Numerous low-to-moderate amplitude slow waves in bilateral hemispheres, sporadic or paroxysmal, predominantly in frontal regions		
Ictal events: No specific clinical events occurred during monitoring		
EEG diagnosis: Moderate abnormal electroencephalogram		

theta waves with poor modulation and preserved bilateral symmetry, indicating diffuse cerebral dysfunction. Numerous persistent low-to high-amplitude slow waves and sharp–slow-wave complexes were present in all leads, consistent with generalized epileptiform discharges. Following intravenous diazepam, sharp–slow waves gradually decreased and sleep rhythms emerged, confirming the presence of epileptiform activity, which was considered a key clinical manifestation of antibiotic-induced neurotoxicity. Based on medical history, clinical findings, EEG, and CT results (ruling out acute neurological lesions), antibiotic-associated neurotoxicity with encephalopathy and seizure was suspected as the primary diagnosis.

In this case, the patient's mental status declined progressively beginning on day 3 after admission, with seizure onset on day 6. After diagnostic evaluation, the neurology team concluded that the seizures were likely a clinical manifestation of antibiotic-induced neurotoxicity. Antimicrobials administered before seizure onset included moxifloxacin (pre-admission), meropenem, teicoplanin, and ceftazidime–avibactam. The association between each agent and seizure activity was evaluated using the Naranjo Adverse Drug Reaction Probability Scale.[10] The Naranjo Adverse Drug Reaction Probability Scale is a validated 10-item tool for assessing the causal relationship between drug exposure and adverse reactions, with each item scored as +1 (yes), 0 (unknown), or −1 (no). The total score ranges from −4 to +9, and the causal relationship is categorized as definite (≥9), probable (5–8), possible (1–4), and doubtful (≤0). The detailed scoring results for each antimicrobial agent administered to the patient are presented in Supplementary Table 2.

Moxifloxacin undergoes primarily hepatic metabolism with minimal renal excretion and has a short elimination half-life. During its administration, the patient remained alert with normal hepatic function, and drug clearance was unimpaired. The interval between moxifloxacin discontinuation and seizure onset was prolonged, and no neurological symptoms occurred during either hospitalization when the medication was used. The Naranjo score was 0, indicating no association with seizure onset.

Meropenem was administered after admission at moderate doses during and after hemofiltration and discontinued on day 3. Seizures occurred 3 days after discontinuation. When meropenem was reintroduced for fever and suspected infection recurrence following withdrawal of the implicated antibiotic, no additional seizures occurred. Meropenem was assigned a Naranjo score of 1, indicating unlikely causation.

Teicoplanin was initiated empirically at admission for 2 days with an appropriate weight-based loading dose. According to the Chinese prescribing information for teicoplanin, loading dose adjustment is not required in critically ill patients with renal insufficiency, regardless of hemodialysis status, and seizure is not listed as an adverse reaction.[11] Teicoplanin has been used clinically for decades without reported seizure cases. Neurological adverse effects primarily

include agitation, delirium, and irritability. Teicoplanin was therefore essentially excluded as a causative agent, with a Naranjo score of 0.

In contrast, findings from Gatti et al indicated that both standard and high doses of CZA-AVI can cause severe central nervous system toxicity, manifesting primarily as cephalosporin-associated encephalopathy and altered mental status.[12] The prescribing information notes that seizures, nonconvulsive status epilepticus, coma, asterixis, neuromuscular hyperexcitability, and myoclonus have occurred in patients receiving ceftazidime, particularly those with renal impairment.[1] In this case, CZA-AVI was initiated on Day 1. Mental status began to decline on treatment day 2, and the dose was increased on day 3 despite incomplete renal recovery. Seizures occurred on day 4, prompting immediate discontinuation of CZA-AVI and initiation of antiepileptic therapy. Following drug withdrawal, both consciousness and seizure activity gradually improved, EEG findings indicated marked recovery, and no recurrence occurred after antiepileptic medications were discontinued. Considering the temporal relationship, clinical characteristics, and exclusion of alternative etiologies, the Naranjo score was 6, indicating a probable association between CZA-AVI-induced neurotoxicity and the subsequent seizure onset (seizure as the primary clinical manifestation of this neurotoxicity).

Mechanisms, Risk Factors, and Management of Ceftazidime–Avibactam–Induced Neurotoxicity

Clinical reports describing neurotoxic adverse reactions associated with CZA-AVI remain limited; however, prescribing information documents severe neurological reactions in patients receiving ceftazidime. Vigilance is therefore essential during its clinical use. The neurotoxicity of CZA-AVI is primarily attributed to its ceftazidime component. Proposed mechanisms of cephalosporin-associated neurotoxicity include antagonism of GABA_A receptors, reduced presynaptic GABA release leading to impaired GABAergic inhibition, endotoxin-mediated release of proinflammatory cytokines such as tumor necrosis factor alpha (a feature of sepsis-associated encephalopathy), glutamate-mediated excitotoxicity, and neurotoxic effects related to side-chain structure, all of which can lead to abnormal neuronal discharges and further trigger seizure, the typical clinical manifestation of such neurotoxicity.[13–16]

Neurotoxicity following beta-lactam antibiotic administration is thought to result from drug accumulation within the central nervous system.[13] Major risk factors for cephalosporin-induced neurotoxicity (which may further manifest as seizure, encephalopathy, or myoclonus) include renal impairment, excessive dosing, and pre-existing neurological disorders. Additional contributing factors include advanced age or very young age, low protein binding, hepatic dysfunction, concurrent use of nephrotoxic or proconvulsant drugs, and cranial trauma.[13–20] Renal dysfunction represents the most critical risk factor.[13,14] These factors collectively increase susceptibility to antibiotic-associated neurotoxicity. Repeated dosing enhances cephalosporin penetration into CSF, and convulsant activity intensifies at higher concentrations.[15] Furthermore, sepsis and critical illness impair blood–brain barrier function, facilitating greater CNS penetration of antibiotics, while these conditions often require higher doses.[18]

A history of CNS disease may also reduce the neurotoxicity threshold for third- and fourth-generation cephalosporins.[16] Typical onset of cephalosporin-induced encephalopathy occurs 1 to 10 days after initiation, with resolution 2 to 7 days following drug withdrawal, a pattern consistent with the present case.[16] The patient was an older critically ill individual with acute kidney injury, hypoalbuminemia, cerebral infarction, and prior exposure to moxifloxacin and meropenem. During incomplete renal recovery and without precise daily creatinine clearance assessment, the CZA-AVI dosage was doubled. These factors likely resulted in excessive ceftazidime concentrations in plasma and CSF, precipitating seizure onset. Although the patient did not receive CRRT during treatment with CZA-AVI, the interval between the end of CRRT and the initiation of CZA-AVI was short. Therefore, the influence of CRRT on the accurate assessment of renal function should still be noted. It is important to note that in this critically ill patient receiving CRRT, the use of the Cockcroft-Gault equation to estimate creatinine clearance (CrCl) has significant limitations, as this equation was not validated in patients under continuous extracorporeal support. The patient's true drug elimination capacity was likely a complex interplay between residual renal function, CRRT prescription, and membrane characteristics. The reported estimated CrCl values should therefore be interpreted with caution and primarily reflect the degree of underlying renal injury rather than a precise guide for drug dosing in this setting. The decision to adjust antibiotic doses

was made based on a combination of the estimated CrCl (as a marker of baseline renal dysfunction), the specific CRRT modality and intensity, and institutional protocol, acknowledging the inherent uncertainty.

A 2022 pharmacovigilance study reported neurotoxic adverse events in 15.62% of CZA-AVI–treated patients, demonstrating stronger neurotoxicity signals compared with meropenem, ceftazidime, or ceftriaxone.[17,21] In addition, CZA-AVI was more frequently associated with encephalopathy and myoclonus than ceftazidime alone, with differing neurotoxicity thresholds.[17,21] These findings indicate that (1) although both meropenem and CZA-AVI contain beta-lactam rings, CZA-AVI may carry greater neurotoxic risk; combined with the Naranjo assessment, this supports a probable causal relationship between CZA-AVI and seizure onset in this patient; and (2) avibactam may possess intrinsic neurotoxic potential or may potentiate ceftazidime-related neurotoxicity. Because both components undergo renal elimination, avibactam may alter ceftazidime pharmacokinetics in the setting of renal impairment, further reducing drug clearance. These possibilities require additional investigation.

When neurological adverse events, particularly seizures, develop, management includes immediate discontinuation of the medication and substitution with non-neurotoxic antimicrobial agents to eliminate the trigger of neurotoxicity, combined with symptomatic treatment with GABA agonists for seizure control to alleviate the clinical manifestations, and consideration of hemodialysis or renal replacement therapy for refractory cases.[14–16] Given the high dialyzability of cephalosporins, with approximately 70% removal achieved after 3 hours of hemodialysis, dialysis effectively reduces serum and CSF drug concentrations.[14–16] In this case, once CZA-AVI–induced neurotoxicity was recognized, the drug was discontinued and propofol was administered for sedation. Subsequent neurological improvement supported the diagnosis of CZA-AVI–associated neurotoxicity.

Prevention and Therapeutic Drug Monitoring

When critically ill patients develop neurological symptoms, drug-induced adverse reactions are seldom considered initially. Clinicians must therefore remain thoroughly familiar with drug indications, dosing recommendations, potential adverse effects, clinical manifestations, high-risk populations, and appropriate management strategies to ensure safe and effective use.

For high-risk patients, neurotoxicity may be prevented through dose adjustment and serum concentration monitoring when feasible.[15] Although CZA-AVI dosing can be modified for renal impairment according to prescribing information (Supplementary Table 3), the absence of established neurotoxicity threshold concentrations, delays in obtaining monitoring results, and substantial interindividual variability complicate timely dose optimization.[1,14] Despite these limitations, therapeutic drug monitoring (TDM) remains valuable for optimizing beta-lactam therapy, particularly during continuous or high-dose regimens.[19] The therapeutic goal of HDCI is maintaining plasma concentrations at 4 to 5 times the MIC while keeping levels below the toxicity threshold for pathogens classified as resistant by standard breakpoints. Because many hospitals lack access to CZA-AVI concentration assays, strict adherence to dosing guidelines and daily monitoring of creatinine clearance with timely dose adjustment are critical for minimizing neurotoxicity risk.

Early recognition is essential for reducing neurotoxic adverse reactions. Clinicians who understand neurotoxicity mechanisms and use continuous EEG monitoring can more readily identify early neurotoxicity and initiate prompt intervention.[15] Careful daily bedside assessment by physicians and vigilant observation by nursing staff, with immediate reporting of neurological changes, remain equally important.

In this case, plasma concentration monitoring and continuous bedside EEG were unavailable. Awareness of the neurotoxic potential of CZA-AVI was insufficient, and daily creatinine clearance monitoring was not performed, limiting opportunities for early prevention. Notably, avoiding neurotoxic agents in high-risk populations is the most effective preventive measure.[16]

Limitations

This case report has several limitations inherent to its design. First, as a single-case report, it describes an association observed in one patient; therefore, it cannot establish a definitive causal relationship between CZA-AVI and the neurotoxic event, and the generalizability of the findings is limited. Second, TDM for CZA-AVI was not performed during the period of neurotoxicity, which precludes correlating the neurological symptoms with specific drug exposure

levels. Furthermore, continuous EEG monitoring was not initiated at the early signs of mental status change, potentially missing subclinical or nonconvulsive seizure activity. The absence of these monitoring modalities, while reflecting real-world constraints in many clinical settings, limits a more precise assessment of the exact onset and the dose–toxicity relationship. Future prospective, multicenter studies incorporating systematic TDM and neurophysiological monitoring are warranted to better quantify the neurotoxic risk of CZA-AVI and establish clearer prevention and management strategies. Importantly, in the context of CRRT, the estimation of renal function using traditional formulas (eg, Cockcroft-Gault) is inherently imprecise and may not accurately reflect drug clearance. The lack of therapeutic drug monitoring (TDM) to guide dosing in this complex scenario is an additional limitation.

Conclusions

This patient, with multiple predisposing risk factors for drug-induced neurotoxicity, developed severe CZA-AVI-induced neurotoxicity (presenting with seizure as the critical clinical manifestation) after receiving the medication, and achieved significant clinical improvement after timely drug discontinuation and targeted management of neurotoxicity and its seizure manifestation. Intensive care physicians should strictly adhere to indications and dosing regimens and sustain heightened awareness of potential CZA-AVI-induced neurotoxicity, as well as its severe clinical manifestations such as seizure, particularly in older critically ill patients with renal impairment, neurological disease, or hypoalbuminemia (high-risk populations for neurotoxicity). Concomitant use of neurotoxic and nephrotoxic agents should be avoided when feasible. Clinicians should closely monitor mental status, utilize EEG and therapeutic drug monitoring when available, and obtain timely specialty consultation to prevent or reduce the risk of severe neurological complications.

Ethical Approval

This case report does not involve any ethical issues or require institutional approval for publication.

Patient Consent Statement

The authors declare to have the written informed consent of the guardian of the patient involved in the reported case to prepare and publish the case report, as the patient was incapacitated.

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Disclosure

The authors declare that they have no competing interests in this work.

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