



Reversible cefazolin-induced status epilepticus in a peritoneal dialysis patient

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ABSTRACT

Cefazolin-induced neurotoxicity with the documented toxic concentration has not been reported in uremic patients on continuous ambulatory peritoneal dialysis (CAPD). We described an elderly female on CAPD for years presented with newly-onset status epilepticus. Her body weight was 60 kg. And she had received intraperitoneal ceftazidime and cefazolin 1.5 g once daily for her CAPD peritonitis 5 days earlier. She was disoriented but afebrile with normal blood pressure. Laboratory data showed WBC 18,480/uL, pH 6.93, HCO₃ 8.5 mmol/L, free Ca²⁺ 3.5 mmol/L, and albumin 2.8 g/dL. Although antiepileptic drugs and hypocalcemia correction ceased the seizure, her consciousness remained semi-coma. Image studies of brain were unremarkable. Despite undetectable serum ceftazidime, her cefazolin trough level was 149.5 µg/mL. Emergent hemodialysis rapidly resolved her neurological features accompanied by a markedly declined serum cefazolin concentration (28.6 µg/mL). Higher intraperitoneal cefazolin dosing in patients on CAPD may cause drug-induced neurotoxicity with status epilepticus which could be rapidly corrected by hemodialysis.

1. Introduction

Seizures are relatively common in patients with renal failure, with an incidence ranging from 10 % to 30 % [1]. Beside its traditional causes, such as structural defects, infectious diseases, genetic defects, and autoimmune disorders, specified risk factors, such as imbalanced electrolytes, and drug-induced neurotoxicity due to decreased renal elimination, are also notable in this vulnerable subgroup [2]. The most common drug-induced neurotoxicity in renal failure involves antibiotics, such as aminoglycosides, penicillin, cephalosporins, and carbapenems; antiviral agents such as acyclovir and valacyclovir; and muscle relaxants such as baclofen [3–5]. Although up to 6 % of new-onset seizures were reported to be drug-related, drug-induced neurotoxicity has still been less appreciated since the diagnosis is often based on the absence of other clear etiologies and definite chronology of the culprit drug administration [6].

Approximately 10–15 % of patients with end-stage kidney disease (ESKD) receive continuous ambulatory peritoneal dialysis (CAPD) to survive and maintain their quality of life. Notably, CAPD-related peritonitis is the most common infectious complication. Empiric intraperitoneal (IP) antibiotics to cover Gram-positive and -negative

microorganisms for CAPD-related peritonitis are often administered prior to Gram staining or culture [7]. For example, intermittent or continuous IP administration of cefazolin and ceftazidime, a combination of first- and third- generation cephalosporins, is widely used. However, the presence of active peritonitis may enhance membrane permeability and thus increase the bioavailability of antibiotics during IP antibiotic administration, resulting in a higher risk of systemic toxicity [8].

Here, we describe an elderly uremic patient with CAPD-related peritonitis who developed status epilepticus caused by cefazolin-induced neurotoxicity after intermittent IP ceftazidime (1.5 g once daily) and cefazolin (1.5 g once daily) administration for 5 days. The patient's abnormal neurological features rapidly resolved with emergent hemodialysis (HD) to effectively reduce the toxic serum cefazolin level (149.5 µg/mL).

2. Case presentation

A 76-year-old female with diabetic nephropathy related to ESKD on CAPD for 3 years presented to the emergency department with altered mental status and generalized seizures. Pertinent history revealed that

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the patient had undergone successful parathyroidectomy for tertiary hyperparathyroidism with renal osteodystrophy 1 month ago and had taken oral calcium acetate and active vitamin D to treat hungry bone syndrome. Five days earlier, the patient was initiated on intermittent IP ceftazidime (1.5 g, 25 mg/kg) and cefazolin (1.5 g, 25 mg/kg) daily at nighttime for CAPD-related peritonitis with abdominal pain and cloudy dialysate. The other concurrent drugs used included bisoprolol and amlodipine for hypertensive cardiovascular disease.

On physical examination, the patient was disoriented (GCS 10) but afebrile, with a blood pressure of 134/76 mmHg and heart rate of 118 beats/min. A pale conjunctiva and tachypnea without rales were also noted. The patient's dialysate effluent had become clean, with white blood cell (WBC) count of 2–3 cells/ μL . Pertinent laboratory data demonstrated WBCs 18,480/ μL , hemoglobin 11.2 g/dL, platelets 262,000/ μL , pH 6.93, partial pressure of oxygen 63.3 mmHg, partial pressure of carbon dioxide 41.6 mmHg, bicarbonate 8.5 mmol/L, serum lactate 25.1 mmol/L, ammonia 501 $\mu\text{g/dL}$, glucose 237 mg/dL, creatine phosphokinase 292 U/L, sodium 137 mmol/L, potassium 3.9 mmol/L, free calcium 3.5 mg/dL, magnesium 2.3 mg/dL, phosphate 4.1 mg/dL, albumin 2.8 g/dL, and C-reactive protein 0.84 mg/dL. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain revealed no significant structural abnormalities. Although epilepsy and moderate hypocalcemia (free Ca^{2+} 3.5 mg/dL) subsided after intravenous calcium administration and antiepileptic drug (AED) use, the patient remained in a semi-coma state. A subsequent electroencephalogram (EEG) clearly showed epileptiform discharges, such as polymorphic sharp waves.

Upon reviewing the patients prescribed drug list, cefazolin and ceftazidime administered IP were suspected to be the offending drugs. The presence of both drugs in the serum was determined using high-performance liquid chromatography. Despite undetectable serum ceftazidime, her serum cefazolin concentration at trough (16 h after night exchange) was considerably high, up to 149.5 $\mu\text{g/mL}$. Without further CAPD, emergent high-flux HD rapidly resolved the neurological disturbances, along with a marked decrease in serum cefazolin level (28.6 $\mu\text{g/mL}$) (Fig. 1). The patient's hospital course was uneventful, with a switch from CAPD to HD in consideration of old age and CAPD-related peritonitis.

3. Discussion

This older adult female undergoing CAPD without prior seizure history developed status epilepticus and altered consciousness after a recent parathyroidectomy with hungry bone syndrome and CAPD-related peritonitis treated with IP antibiotics. With the exclusion of other identifiable causes, such as alcohol consumption, metabolic or endocrine causes, trauma, infection, and organic brain lesions, rapid elimination of the toxic serum trough level of cefazolin with full

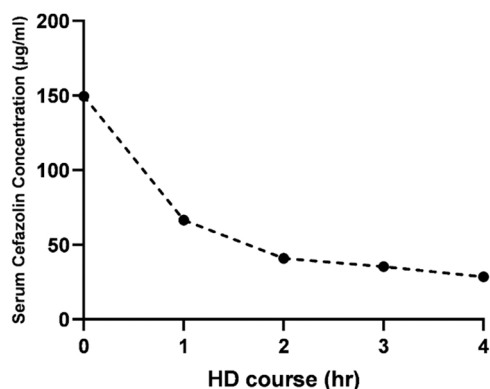


Fig. 1. Serum cefazolin concentrations during hemodialysis (HD) course. Abbreviation: HD, hemodialysis, hr, hour.

recovery from neurological abnormalities by prompt HD supported the diagnosis of cefazolin-induced neurotoxicity. To the best of our knowledge, this is the first case of cefazolin-induced neurotoxicity with documented serum toxic concentration in uremic patients undergoing CAPD [9,10].

Clinically, antibiotic-induced neurotoxicity can be classified into three types: type 1 (associated with seizures and myoclonus), type 2 (associated with psychosis and delirium), and type 3 (associated with cerebellar dysfunction). Cephalosporins and penicillin are generally associated with type 1 neurotoxicity [3]. Cephalosporin-induced neurotoxicity, although rare but well-documented, has been frequently reported in patients with renal function impairment since, similar to penicillin, it is primarily eliminated from the kidneys [3]. Among all generations of cephalosporins associated with neurotoxicity, cefepime is the most commonly reported drug, while ceftriaxone, ceftazidime, cefotaxime, and cefazolin have also been mentioned [11]. Its neurotoxicity is highly related to the suppression of inhibitory postsynaptic responses, predominantly mediated through the inhibition of γ -amino butyric acid (GABA_A) receptor function [12]. The epileptogenic reaction of cephalosporins correlates with the molecular size of the substituents at positions 7 (R1) and 3 (R2) of their 7-cephalosporanic acid structure. Cefazolin with two heterocyclic rings at positions 7 and 3 may exert potentially higher epileptogenic activity [13].

In this patient, the dosage of IP cefazolin 1.5 g (25 mg/kg) once exchange overnight per day appeared to be relatively higher than the recommended dose (1 g or 20 mg/kg per day) [7]. Moreover, the presence of active peritonitis may have enhanced IP membrane bioavailability, leading to greater absorption of cefazolin. Based on the prior pharmacokinetic study of IP cefazolin (2.5 gm) administration in patients undergoing CAPD, the plasma concentrations of cefazolin were $96.9 \pm 9.4 \mu\text{g/mL}$ at 10 h and gradually decreased to $79.8 \pm 7.3 \mu\text{g/mL}$ at 24 h [14]. Our patient's trough serum cefazolin concentration was up to 149.5 $\mu\text{g/mL}$, reaching a toxic level. In the setting of hypoalbuminemia, decreased protein binding of cefazolin increased the free fraction of drug in the cerebrospinal fluid (CSF), and reduced protein glycation and carboxylation altered the integrity of the blood–brain barrier, enhancing cefazolin entry into the central nervous system (CNS) [8,15,16]. Hence, the higher blood antibiotic level in this patient resulted in a higher CSF concentration. Hypocalcemia found in this patient also reduced the threshold of neuronal excitability, in addition to well-known risk factors for antibiotic-induced neurotoxicity, such as advanced age (> 70 years), renal failure, and malnutrition [3].

The key treatment for cefazolin-induced seizures is rapid elimination of the accumulated culprit drug in addition to antiepileptic treatment. Given its structural and pharmacokinetic properties of lower molecular weight (476.5 Da) and volume of distribution ($0.20 \pm 0.05 \text{ L/kg}$), HD is superior to PD in cefazolin elimination (the half-life of cefazolin is 2.65–4.95 h in HD vs. 11.4 h in CAPD) [15,17]. Emergent high-flux HD for 4 h achieved a rapid decline in serum cefazolin level from 149.5 to 28.6 $\mu\text{g/mL}$ and shortened the recovery time from cefazolin-induced neurotoxicity.

4. Conclusion

In summary, our case highlights that IP cefazolin administration in patients with CAPD-related peritonitis may cause drug-induced neurotoxicity with status epilepticus, especially in patients associated with more risk factors. Prompt HD to remove the culprit drug and resolve life-threatening neurotoxicity relies on early recognition to avoid unnecessary workup. More attention should be paid to drug dosing to avoid drug-induced toxicity in patients undergoing CAPD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Data availability

Data will be made available on request.

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