Cefoperazone-Sulbactam Associated Refractory Seizures

Sir,

A 34-year-old male presented with recurrent focal facio-brachial seizures with and without bilateral tonic-clonic convulsions. He had chronic kidney disease (secondary to focal segmental glomerulosclerosis), was a renal transplant recipient, and was on immunomodulatory treatment (basiliximab, mycophenolate mofetil, cyclosporine, prednisolone) for 2 years.

The seizure semiology consisted of repetitive brief facio-brachial seizures with and without bilateral tonic-clonic convulsions lasting for 40 seconds to 2 minutes. Prior to admission at our hospital, he was initially admitted to a nephrology hospital, for acute gastroenteritis and was treated with ciprofloxacin in a dose of 500 mg twice a day. His baseline serum creatinine...
level was 3 gm/dl with an estimated glomerular filtration rate (eGFR) of 30 ml/min/1.73 sq. m. During the course of his hospitalization there, he developed one episode of focal seizure with bilateral tonic-clonic convulsions, for which he was loaded with injection sodium valproate 1 gm, which was continued in a dose of 500 mg twice a day. Ciprofloxacin was stopped and replaced by injectable cefoperazone-sulbactam in a dose of 3 gm twice a day. Also, phenytoin was initiated at a dose of 300 mg/day. Despite that, he had persistent recurrent focal seizures and so was referred to our hospital. In the emergency department of our hospital, he had recurrent facio-brachial seizures and so levetiracetam 1500 mg/day and cllobazam 10 mg twice a day was added. His hemogram, electrolytes, thyroid, and hepatic functions, magnetic resonance imaging brain, and electroencephalography (EEG) were normal. Because of persistent focal seizures, the dose of cllobazam was increased from 20 mg/day to 30 mg/day and lacosamide 200 mg/day was added. Despite being on an optimal therapeutic dose of all anti-seizure drugs, he continued to have 10-12 episodes of focal facio-brachial seizures per day. Cerebrospinal fluid (CSF) was normocellular, with normal protein and glucose and negative cytology. Serum and CSF autoimmune panel [Anti VGKC Complex (LG1, CASPR2), NMDAR, TPO Ab, GAD, GABABR, and AMPAR] were negative. Serum cyclosporine level was normal (276 ng/mL, with a normal reported range of 100-400 ng/mL). After ruling out structural, metabolic, vascular, infective, autoimmune etiologies a possibility of drug/toxic etiology was considered. He was receiving cefoperazone-sulbactam and so a possibility of antibiotic-associated seizure was considered. He had baseline renal dysfunction, which is a known risk factor for antibiotic-associated neurotoxicity. It was likely that his seizures, initiated by ciprofloxacin were sustained due to the neurotoxicity of cefoperazone-sulbactam. His blood, urine, and stool culture were also negative. Hence, cefoperazone-sulbactam was also stopped. After 48 hours of stopping the antibiotics, the seizures completely stopped. Naranjo’s criteria score for our patient was 7 suggesting a probable association of seizures to cefoperazone-sulbactam use. He was discharged after observation for 5 days. The patient has been on regular follow up with us since then. After six months of seizure-free period, all his anti-seizure drugs have been tapered off gradually and he has been seizure-free without medicines.

**Antibiotic-associated neurotoxicity can be of 3 types:** Type 1 (associated with seizures and myoclonus); type 2 (associated with psychosis and delirium) and type 3 (associated with cerebellar dysfunction).[^1] Cephalosporins are generally associated with type 1 neurotoxicity. Commonly known side effects of cephalosporins include hypersensitivity, gastrointestinal and hepatobiliary disturbances but neurotoxicity is less common. Neurotoxicity can manifest rarely in patients with renal dysfunction, baseline neurological abnormalities and old age. Cephalosporins disrupt inhibitory synaptic transmission which leads to excitotoxicity, manifesting as seizures and myoclonus. Cephalosporins inhibit the ligand-gated ion channel g-aminobutyric acid (GABAAR), leading to a reduced intracellular influx of chloride ions by endogenous GABA, leading to a reduction of the threshold for occurrence of seizures. Renal insufficiency increases the risk of antibiotic neurotoxicity by increasing serum antibiotic concentrations (by reduced urine excretion of antibiotics and by causing proteinuria leading to low albumin, leading to higher antibiotic bioavailability). The higher antibiotic bioavailability leads to higher CSF concentrations of cephalosporins, further potentiating the neurotoxicity. Suzuki and colleagues assessed serial plasma and CSF concentration of ceftriaxone in a patient with encephalopathy in the setting of renal dysfunction. Higher serum and CSF levels of ceftriaxone were present at the time of encephalopathy, which improved post dialysis and was associated with improvement in sensorium.[^2]

Cefazolin, Ceftazidime, Ceftriaxone, Cefepime, and Cefuroxime are described to be associated with neurotoxicity in the form of focal seizures/myoclonic jerks/generalized tonic-clonic seizure/status epilepticus/non-convulsive status epilepticus, encephalopathy, asterixis and global aphasia.[^3][^4] However, the cefoperazone-sulbactam combination has been rarely reported to cause seizures. Our case highlights the rare and lesser-known adverse reaction of the cefoperazone-sulbactam combination. Xiao and Han Qi et al. have reported a patient with community-acquired pneumonia, treated with cefoperazone-sulbactam to develop refractory seizures which recovered after stopping cefoperazone-sulbactam.[^5] The major mode of excretion of cefoperazone is through hepatic clearance, however, 15-36% of it is excreted in the urine. Hence dose adjustment according to creatinine clearance is required in patients with renal dysfunction. The half-life of sulbactam is up to 1 hour and 75% is excreted unchanged in the urine. The co-administration of sulbactam with cefoperazone does not have any effect on the kinetics of either antibiotic or sulbactam.[^6]

Our case highlights the importance of considering cefoperazone-sulbactam as a rare cause of refractory seizures in patients with baseline renal dysfunction.

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**Abbreviations:** LG11, Leucine-rich glioma inactivated-1; CASPR2, Contactin-associated protein like-2; NMDAR, N-methyl-D-aspartate receptor; GAD, Glutamic acid decarboxylase; GABA<sub>R</sub>, Gamaaminobutyric acid receptor; VGKC-Complex, Voltage gated potassium channel; AMPAR,
α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; TPO, Thyroid peroxidase antibody

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial(s) will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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