Cefepime-induced neurotoxicity in a patient with coronary artery bypass

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Abstract:
We present here a case of 58-year-old male operated for coronary artery bypass graft surgery with four grafts. He developed neurologic symptoms with injection cefepime which recovered after withdrawal of the drug.

Key words:
Cefepime, compromised renal function, convulsions, neurotoxicity

Cefepime, a fourth generation cephalosporin, is frequently used antibiotic in post operative patients after CABG. Hence, clinicians should be vigilant about all adverse effects while prescribing cefepime. We report a case of a 58-year-old male with neurotoxicity induced by injection cefepime.

Case Report

A 58-year-old male with a known case of unstable angina came to the multispeciality cardiac hospital. Coronary angiography showed left main carotid artery and left anterior descending artery block; two-dimensional echocardiogram found normal left ventricle function. Right internal carotid artery (ICA) 40% and left ICA 45% stenosis were diagnosed by carotid Doppler. He underwent coronary artery bypass graft (CABG) surgery with four grafts. Intraoperative and immediate postoperative period was uneventful. On the 1st postoperative day (POD) morning, SpO2 dropped to 90% with high inspiratory pressure. The patient had right side pneumothorax on chest X-ray (CXR) examination. Hence, ICD tube was inserted. The patient had 800 ml leg drain and therefore taken for re-exploration of a leg wound. He was prescribed injection cefepime 2 g intravenous (IV) 12 hourly, injection amikacin, tablet aspirin 75 mg OD, clopidogrel 150 mg OD, rosuvastatin 10 mg OD, frusemide 40 mg OD, ranitidine 150 mg OD, tramadol 50 mg, paracetamol 500 mg, liquid paraffin 15 ml, and inotropic support as and when required.

He had difficulty in weaning on the 2nd POD, CXR (P/A) suggested persistent right side pneumothorax. Hence, ICD was re-inserted and thereafter patient was extubated. On the 6th POD morning, he became drowsy, lost orientation to time place and person, and not responded to verbal command. On examination, the patient followed verbal command intermittently and his muscle power IV/V, planter extension. The patient developed focal convulsions in the right upper arm and facial twitching which was independent. Central nervous system (CNS) examination revealed no other abnormality. The neurologist was consulted. Liver function test, computed tomography scan and magnetic resonance imaging brain, cerebrospinal fluid (CSF) examination, arterial blood gas with electrolyte, serum ammonia, and culture (blood, sputum, and CSF) were within normal limits. Patient’s creatinine clearance was <60 ml/min. EEG was not done due to technical difficulty. Injection fosphenytoin IV was given for convulsions, but facial twitch persisted. Injection cefepime was withdrawn. The overall CNS condition of patient remained same, and facial twitching still persisted. The patient became oriented to person from the 11th POD though he was not oriented to time and place with intermittently obeying verbal commands. The patient recovered over time and on the 15th POD he was fully conscious, alert, and oriented to time, place, and person with obeying verbal command. Patient shifted to ward on the 15th POD. The patient recovered without particular sequel and got discharged on the 17th POD.

Discussion

Cefepime is a parenteral fourth-generation cephalosporin antibiotic with an extended
spectrum of antimicrobial activity, active against many Gram-positive and Gram-negative bacteria. It is excreted primarily unchanged in the urine. Its half-life increases as renal function declines and may result in adverse drug events.\[^1\]

Neurotoxicity is common among many groups of antibiotics in at-risk patients and can range from ototoxicity, neuropathy and neuromuscular blockade to confusion, nonspecific encephalopathy, seizures, and status epilepticus. Neurotoxicity has been reported with cefazolin, cefuroxime, ceftazidime, and cefepime. Confusion, agitation, myoclonic jerks, seizures, and coma are clinical features of cefepime-induced neurotoxicity. Patients with old age, decreased renal clearance of drug, increased free antibiotic levels in plasma, critical illness and increased drug penetration in brain, and high doses (>4 g/day) are predispose to cefepime-induced encephalopathy.\[^2\]

Chatellier et al. found when serum concentration available, cefepime level was mostly above 30 μg/mL in dialysis patients.\[^2\] Thus, avoidance of neurotoxic agents in patients with the above-mentioned risk factors is critical in preventing neurotoxicity.\[^2\]

Time relationship for cefepime neurotoxicity is 20 h to 5 days of drug exposure.

According to the WHO causality assessment criteria,\[^3\] in this case, the neurotoxicity was probably due to cefepime as other causes for convulsions had been ruled out by various investigations. Moreover, adverse reactions are rarely specific for the drug without specific diagnostic tests, and a rechallenge is rarely ethically justified. In this case, according to the objective causality assessment by the Naranjo probability score, the causal association between neurotoxicity and cefepime was probable (Naranjo score = 5).\[^4\]

Sugimoto et al. also demonstrated that the cephalosporin-induced convulsion is mediated predominantly through the inhibition of gamma-aminobutyric acid A receptors and not through N-methyl-D-aspartate receptor modulation The authors used seven different cephalosporins including cefepime and examined their convulsive activities using both in vivo and in vitro models.\[^5\] The most widely accepted theory of the pathogenesis of convulsions induced by penicillin and related \(\beta\)-lactam compounds involves the interference or inhibition of GABA binding to GABAA-R.\[^5\] Other possible mechanisms for cephalosporin neurotoxicity could be induction of endotoxins and glutaminergic mechanisms. Various studies also showed that cephalosporins with high affinity for GABAA-R and those with high penetrance through the blood-brain barrier are more neurotoxic.\[^5\]

### Conclusion

Drug-induced neurotoxicity should be considered when an elderly patient with a compromised renal function on cefepime develops progressive neurologised symptoms. However, an actual pathophysiological mechanism implicated in causation is not yet understood completely. Further in vitro and in vivo studies related to cefepime and GABA system interactions are required. Dosage adjustment and substitution with less neurotoxic antibiotic from same or other drugs in patients with renal insufficiency has been recommended to prevent adverse drug events. Meanwhile, diligent vigilance by health-care providers is required to early recognize and prevent potential neurotoxic effects.

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### Conflicts of Interest

There are no conflicts of interest.

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