Overview of Neurotoxicity of Beta-Lactam Therapy

Madeleine King, PharmD
PGY1 Pharmacy Practice Resident

Beta-lactam antibiotics are well established in clinical practice as a mainstay of therapy and are commonly prescribed for a wide variety of Gram positive and negative infections. Although hypersensitivity reactions are the main adverse drug reaction reported with beta-lactam antibiotics, they also can pose a risk for central nervous system (CNS) toxicity.[2] Neurologic symptoms present as a wide spectrum ranging from altered mental status and confusion to status epilepticus. Risk factors for developing neurotoxicity include renal insufficiency, elderly age, underlying CNS disorder, and CNS infection.

The mechanism through which beta-lactams can cause neurotoxicity is thought to be related to the chemical structure of the beta-lactam ring and its effects on gamma-aminobutyric acid (GABA) neurotransmission. Beta-lactam antibiotics are able to bind directly to the GABA-A receptor due to their structural similarity. This subsequently leads to decreased GABA release, increased excitatory neurotransmission, and lowering of the seizure threshold. Cephalosporins exhibit competition inhibition of the GABA-A receptor, whereas penicillins exhibit non-competitive inhibition. Therefore, cephalosporins have increased potential for causing neurotoxicity.[1,2]

A review of cefepime-associated neurotoxicity published in Critical Care in 2017 by Payne et al identified 135 patients with reported CNS effects with cefepime therapy. The median age was 69 years old, and 80% of patients had concurrent renal dysfunction. Neurotoxic effects typically started 4 days after initiation of cefepime. Symptoms were progressive in nature, and drug discontinuation led to clinical resolution in the majority of cases. Initially, symptoms presented as altered mental status but led to myoclonus and seizures in 13% of patients. 48% of patients received higher doses than recommended for renal function, and 26% of patients had unreported dosing regimens. Renal dysfunction and elevated concentrations of cefepime were major risk factors identified. Cefepime is 85% excreted unchanged by the kidneys, so renal dysfunction leading to reduced cefepime clearance can significantly increase active serum concentrations of cefepime. In addition, ICU patients are at increased risk of increased CNS penetration due to inflammatory conditions leading to changes in blood-brain-barrier permeability.[3] Neurotoxic effects have also been shown to occur with other cephalosporins including ceftazidime, cefazolin, and cefuroxime. Cefepime and ceftazidime had comparatively less affinity for GABA-A than cefazolin, but they appear to have more neurotoxic effects potentially due to differences in CNS penetration.[2]

Beta-lactam neurotoxicity is a significant side effect that should be considered. However, the majority of patients identified in case reports were elderly patients with impaired renal function receiving higher than recommended antibiotic doses. Adjustment of beta-lactam dosing during renal failure should be carefully evaluated to limit the potential for development of neurotoxic effects.

References

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