Cefepime-Induced Encephalopathy, Single-Center Incidence, Complexities in Diagnosis

To the Editor—We read with interest the recent review from Appa et al. titled "Characterizing Cefepime Neurotoxicity: A Systematic Review" [1]. As a result of increasing concern for cefepime as a possible etiology for cases of encephalopathy, we investigated the overall incidence of this toxicity at our medical center from January 2016 to May 2017. Similar to the published study, we summarized patient characteristics of those with suspected cefepime-induced encephalopathy (CIE). Unique to our analysis, we included an assessment of other potential etiologies of encephalopathy at the time of symptom onset and the consequences of antibiotic therapy change.

Out of 4446 patients receiving cefepime, there were 18 (0.4%) requests to change cefepime to an alternative antipseudomonal agent as a result of concern for CIE. This represents an incidence of 1 in 250 courses of cefepime. Upon review of these 18 cases, in only 3 (0.07%), or 1 in 1429 courses, was it evident that following cessation of cefepime (as the primary intervention) symptoms resolved. The remaining patients had other identified causes (n = 7) or symptoms did not improve following cefepime discontinuation alone (n = 8).

Similar to Appa et al. and other studies reporting cases of CIE, the 3 patients with likely CIE in our study were older (range, 64–80 years) and had some degree of renal insufficiency (creatinine clearance range, 17–59 mg/dL) [1–4]. However, all patients were receiving appropriate doses for their renal function at the time of symptom onset. Patients developed symptoms consistent with CIE within 4–5 days of cefepime initiation, and symptoms resolved within 3–4 days of cefepime discontinuation. Additionally, all 3 patients had electroencephalogram (EEG) patterns with triphasic waveforms (TWFs).

Among the 18 patients with suspected CIE, the average number of additional potential etiologies for encephalopathy was 4.8 (range, 3–9). Specifically, among the 3 patients with likely CIE, the number of additional etiologies ranged from 3 to 6. Other potential etiologies included baseline neurologic abnormalities, microvascular ischemic disease, other medications known to cause symptoms consistent with encephalopathy, uremia, sepsis/severe infection. Of interest, 6 (33%) patients with suspected CIE were changed to inferior and/or more toxic antibiotic regimens. Five patients received a more toxic antibiotic (eg, patient with baseline prolonged QTc interval who was started on ciprofloxacin or who required the addition of vancomycin). Three patients required an additional agent be added (eg, changed to aztreonam and vancomycin combination), and 1 patient was changed to piperacillin-tazobactam, which was not active against their *Enterobacter* infection.

Similar to other studies, the primary limitation of our analysis is the difficulty of diagnosing CIE. While EEG findings are helpful in making this diagnosis, TWFs are not specific to cefepime. Rather, it is a consistent finding among patients with toxic or metabolic encephalopathy and structural encephalopathy, with the 3 most common causes being hepatic encephalopathy, renal failure, and anoxic brain injury [5]. Additionally, we observed a high number of other potential causes of encephalopathy among our index patients. Pinpointing cefepime as the primary cause of encephalopathy is a clinical challenge. What is possibly evident from this observation is that while cefepime alone may not be a definitive cause, perhaps it is the combination of cefepime among high-risk patients that may result in encephalopathy.

Our data are consistent with the data provided by Appa et al., suggesting that encephalopathy is a possible, but uncommon reported toxicity with cefepime use. This toxicity is noted to occur primarily among elderly patients with reduced renal function. However, our analysis highlights the high potential for confounders when making a CIE diagnosis, as multiple etiologies for encephalopathy are often present among inpatients requiring broad-spectrum antibiotics. Additionally, given the limited amount of antipseudomonal agents available, patients with suspected CIE may be at increased risk for suboptimal antibiotic therapy. Consequently, prior to cefepime discontinuation due to suspected CIE, clinicians should carefully consider the risks of potentially selecting an inferior or more toxic antibiotic regimen.

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