

ALTERNATIVE VIEWPOINTS

New Insights On Cefepime Associated Neurotoxicity

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In their interesting paper, Lam and Gomolin extensively discussed about cefepime induced neurotoxicity in humans throughout a case report and a literature review.¹ We would like to make some further comments in addition to the information provided. The authors reported a total of 48 cases (MEDLINE literature search: 1966–2005) of adverse neurological effects in patients who had renal insufficiency. We have been monitoring cefepime associated neurotoxicity since we published a case report.² In the same period we found 14 additional cases of cefepime associated neurotoxicity in patients with renal failure.^{3–7} Additionally we also found 6 cases of cefepime associated neurotoxicity in the absence of reduced renal function.^{4, 6, 8} Furthermore, recently one case of cefepime associated neurotoxicity has also been observed in an adult without renal failure who developed a generalized nonconvulsive status epilepticus (NCSE) due to cefepime.⁹ To our knowledge, at least 70 cases of cefepime associated neurotoxicity have been reported to date (7 without renal failure) in a total of 24 publications.

We agree with authors about the predisposing factors (i.e., renal failure) for cefepime-induced neurotoxicity. Moreover delayed encephalopathy and NCSE may appear in the absence of renal failure, due to overdose or inter-individual pharmacokinetic/pharmacodynamic differences. Independently, the final mechanism of the

adverse reaction may involve augmented concentrations of cefepime in cerebral spinal fluid (CSF). This could low seizure threshold, reducing the GABA-mediated inhibitory response through inhibition of GABA(A)-receptor function.¹⁰

As the authors stated, if a patient on cefepime develops neurological symptoms, drug neurotoxicity should be considered. However, physicians should be aware of cefepime induced neurotoxicity not only with renal failure but with normal renal function as well. This may be particularly true in the elderly.

References

1. Lam S, Gomolin IH. Cefepime neurotoxicity: Case report, pharmacokinetic considerations, and literature review. *Pharmacotherapy*. 2006;26:1169–74.
2. Abanades S, Nolla J, Rodriguez-Campello A, Pedro C, Valls A, Farre M. Reversible coma secondary to cefepime neurotoxicity. *Ann Pharmacother* 2004;38:606–08.
3. Chow KM, Wang AY, Hui AC, Wong TY, Szeto CC, Li PK. Nonconvulsive status epilepticus in peritoneal dialysis patients. *Am J Kidney Dis*. 2001;38:400–05.
4. Diemont W, MacKenzie M, Schaap N, et al. Neuropsychiatric symptoms during cefepime treatment. *Pharm World Sci*. 2001;23:36.
5. Plensa E, Gallardo E, Ribera JM, Batlle M, Oriol A, Costa J. Nonconvulsive status epilepticus associated with cefepime in a patient undergoing autologous stem cell transplantation. *Bone Marrow Transplant*. 2004;33:119–20.
6. Bragatti JA, Rossato R, Ziomkowski S, Kliemann FA. Cefepime-induced encephalopathy: clinical and electroencephalographic features in seven patients. *Arq Neuropsiquiatr*. 2005;63:87–92.
7. Fernandez-Torre JL, Martinez-Martinez M, Gonzalez-Rato J, et al. Cephalosporin-induced nonconvulsive status epilepticus: clinical and electroencephalographic features. *Epilepsia*. 2005;46:1550–52.
8. Capparelli FJ, Diaz MF, Hlavnika A, Wainsztein NA, Leiguarda R, Del Castillo ME. Cefepime- and cefixime-induced encephalopathy in a patient with normal renal function. *Neurology*. 2005;65:1840.
9. Maganti R, Jolin D, Rishi D, Biswas A. Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. *Epilepsy Behav*. 2006;8:312–14.
10. Sugimoto M, Uchida I, Mashimoto T, et al. Evidence for the

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involvement of GABA(A) receptor blockade in convulsions induced by cephalosporins. *Neuropharmacology*. 2003;45:304-14.

Authors' Reply

We appreciate the comments of Dr. Abanades and associates and feel that the additional cases contribute to the notion that neurotoxicity almost always occurs when doses are high and/or inappropriate to the patients' renal function. In the report by Diemont et al,¹ five of the six patients received doses of 6 grams daily which is indicated only for patients with febrile neutropenia. The sixth patient received 3 grams daily, but had reduced renal function. Usual doses for infections in patients with normal renal function are 1 to 4 grams daily.² We feel that the higher doses could result in excess cefepime levels, but levels were not reported in these patients. In addition, one of these patients (estimated creatinine clearance [CrCl] = 88 ml/min) recovered from visual hallucinations despite continuation of cefepime therapy. Another patient (CrCl = 97 ml/min) experienced one day of nightmares, visual hallucinations and cerebellar dysfunction which did not recur upon re-challenge. No cefepime levels or electroencephalograms (EEG) were reported. One patient with normal renal function (CrCl = 91 ml/min) did experience nightmares, anxiety, agitation, confusion and hallucinations while receiving 6 grams daily.

Bragatti et al³ described seven patients with reversible cefepime-induced encephalopathy with a peculiar EEG pattern. Regrettably, we excluded this paper from our review because it was published in Portuguese. In the case report by Capparelli et al,⁴ cefepime induced encephalopathy occurred in an 85-year-old man with mild renal impairment (measured CrCl = 75

ml/min).

Abanades also cites a case of nonconvulsive status epilepticus in a 79-year-old woman with normal renal function (reported serum creatinine level = 1.2).⁵ However, this patient's renal function was, in fact, reduced with an estimated CrCl less than 45 ml/min using the Cockcroft & Gault formula.⁶ Serum creatinine concentration alone is a poor estimator for renal function. Older adults may have reduced renal function despite having serum creatinine levels in normal reference range.

We agree with Dr. Abanades and associates that cefepime neurotoxicity might occur in patients with normal renal function, especially when the high dosages are used. We concur that cefepime toxicity should be suspected whenever a patient on cefepime develops unexplained neurological or psychiatric symptoms regardless of renal function.

References

1. Diemont W, MacKenzie M, Schaap N, et al. Neuropsychiatric symptoms during cefepime treatment. *Pharm World Sci*. 2001;23:36.
2. Bristo-Myers Squibb Company. Maxipime (cefepime) package insert. Princeton, NJ; December 2003.
3. Bragatti JA, Rossato R, Ziomkowski S, Kliemann FA. Cefepime-induced encephalopathy: clinical and electroencephalographic features in seven patients. *Arq Neuropsiquiatr*. 2005;63:87-92.
4. Capparelli FJ, Diaz MF, Hlavnika A, Wainsztein NA, Leiguarda R, Del Castillo ME. Cefepime- and cefixime-induced encephalopathy in a patient with normal renal function. *Neurology*. 2005;65:1840.
5. Maganti R, Jolin D, Rishi D, Biswas A. Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. *Epilepsy Behav*. 2006;8:312-14.
6. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

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