

Short Communication

A Mini-Review: Is Cefepime Really Neurotoxic?

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Abstract

There has been a great deal of concern regarding Cefepime neurotoxicity. Research has shown that using Cefepime in the ICU has significant adverse effects. Here, using the literature available on Medline, we summarize the essential parameters and risks associated with Cefepime utilization in the ICU setting.

Keywords: Cefepime; Adverse Effects; Neurotoxicity; ICU; Delirium

Cefepime causes neurotoxicity because it can cross the blood-brain barrier and exhibit GABA antagonism [1]. Symptoms include decreased consciousness, aphasia, encephalopathy, myoclonus, seizures

and coma [1]. Up to 15% of pts in in ICU can have these symptoms [2]. Known risk factors include renal dysfunction, excess dosing, pre-existing brain injury, elevated Cefepime levels [1]. We did a simple search with Medline while utilizing the phrase “cefepime neurotoxicity.” Our query provided us with 95 results. However, we selected the top search results but specifically excluded case reports and observational studies. Here, we summarize the results of those studies for a comprehensive but simplified understanding of Cefepime-induced neurotoxicity.

Payne et al conducted a systematic review from 37 citations by using search engines CINAHL and MEDLINE. They found that majority of cases involved renal dysfunction (80%) and ICU care

(81%) [1]. The median age was 69. In addition, it was noted that all patients had altered mental status with 73% having abnormalities on EEG, 47% with reduced consciousness and 42% with myoclonus [1]. Another important note from the study was that 48% of patient that experienced neurotoxic side effects were overdosed [1]. Similarly, Appa et al from the University of Washington Department of Neurology conducted a systematic review using Library, MEDLINE/PubMed, EMBASE and Scopus. Additionally, they analyzed cases at their own medical center from 1/2013- 6/2016 [3]. They found comparable results with 87% of patients who exhibited symptoms having renal dysfunction and mean age being 67 [3]. Furthermore 40% had myoclonus and 47% had disorientation or agitation [3].

Renal failure tends to be a key risk factor for Cefepime neurotoxicity. Sonck et al conducted a retrospective review of eight patients admitted at their hospital between June 1999 and October 2006 [4]. All eight were diagnosed with renal insufficiency and developed neurological symptoms while being treated with Cefepime [4]. Unfortunately, all eight patients expired within a short time frame after symptomatic presentation [4]. Although they were not able to establish a clear relationship between neurotoxicity and mortality, they do recommend cessation of Cefepime when patients present with aphasia or neurotoxicity [4]. On the other hand, Fugate et al performed a retrospective study of 100 adult ICU patients with at least three days of treatment with Cefepime between January 2009 and December 2011 [5]. They assessed for causality using a modified Delphi method [5]. They found that chronic kidney disease was present in thirty patients

of which ten developed neurotoxicity (p-value of 0.042) [5]. In addition, they also found that Cefepime neurotoxicity tends to occur more when dosage is not renally-adjusted (p-value of 0.001) but can also occur in small fraction of patients despite renal adjustment [5].

The risk of cefepime-induced neurotoxicity increases if patient has renal dysfunction, but it may not depend on severity range. In 2019, a team from Rush University selected patients between January 2014 and July 2018 who had received cefepime for > 48 hours and CrCl < 60 in the ICU setting [6]. They further stratified groups by degree of renal dysfunction [6]. Moderate renal dysfunction patients received <8 g or > 8 g within first 48 hours, and severe renal dysfunction patients received < 4 g or > 4 g in the first 48 hours [6]. They found that the total dose of Cefepime in first 48 hours was higher in the high-dose group, but neurotoxicity occurrence was similar between low and high dose groups with moderate renal dysfunction [6]. In severe renal dysfunction, the higher dose group did have numerically greater frequencies of cefepime-induced neurotoxicity [6].

Despite neurotoxicity, Cefepime may still be a safe medication under the guidance of trough or steady-state levels [7]. A retrospective cohort study from Switzerland studied for correlations between Cefepime trough levels and neurotoxicity [7]. The study involved a sample size of 319 individuals, of which 72 were found to have had symptoms [7]. No neurological side effects were seen in trough levels < 7.7; and levels > 38.1 unanimously exhibited symptoms [7]. The team concluded that when treating patients with Cefepime, a goal trough level

of < 7.7 should be kept in mind in order to avoid neurotoxic effects [7]. Cefepime and plasma trough levels were further studied in an Australian retrospective study [8]. The team utilized all adult patient administered Cefepime between October 2017 and May 2018, and designed a receiver operation characteristic curve of different Cefepime trough plasma concentrations [8]. Of the 259 courses of Cefepime that were administered, approximately 64 courses had trough concentration levels measured [8]. Results showed that trough concentrations of greater than 36 mg/L were most sensitive and specific towards signifying neurotoxicity [8].

There is limited data concerning continuous infusion of Cefepime and effects of neurotoxicity, but it may be a safer option in those with renal dysfunction [9]. A team from Belgium evaluated continuous Cefepime infusion as they were trying to define the threshold above to which neurotoxicity occurs [9]. They conducted a single-center retrospective cohort study which looked all adult patients who underwent at least one Cefepime therapeutic drug monitoring and were treated with CI of 4 grams per day between January 2017 and January 2019 [9]. The study included 98 patients with 201 TDMS [9]. Incidence was 14.3%. Patients who developed neurotoxicity more often had underlying brain disease (35.7%) and had higher steady state concentrations (71.8 +/- 32.9) [9]. They also performed a receiver operating characteristic curve analysis which yielded a cefepime steady-state concentration of 63.2 as cut off point between patients with and without neurotoxicity [9]. Mean steady state was 46.4 when dosages of cefepime were adapted to renal function [9]. They concluded that a dose of 4 grams per day of Cefepime adapted to renal function infused over 24

hours was the best trade-off for risk/benefit ratio if treating empirically [9].

In addition to neurotoxicity, non-convulsive status epilepticus and metabolic encephalopathy have also been reported with Cefepime. Li et al conducted a case control study among medical records at tertiary medical center in Taiwan between 2007 and 2016 [10]. Of the 42 patients identified with cefepime-induced neurotoxicity, approximately 64% were noted to have NSCE on EEG reading with most common pattern being generalized periodic discharge [10]. They also identified that risk factors for Cefepime neurotoxicity include longer duration of Cefepime administration and hemodialysis [10]. Triplett et al conducted a literature review of EEGs among patients with Cefepime neurotoxicity using MEDLINE [11]. They found 37 EEGS samples with three being uninterpretable, one showing generalized epileptiform and 33 showing triphasic waves [11]. In addition, they also performed a retrospective chart review of EEG findings in patients with Cefepime neurotoxicity [11]. They identified 11 patients at their hospital all of whom had abnormal EEGs, with clinical seizure found in one patient and myoclonus in six patients [11].

In conclusion, our brief literature review shows that Cefepime can cause neurotoxic symptoms specifically encephalopathy, myoclonus, chorea-athetosis, convulsions or aphasia. Risk factors seem to be older age, longer duration of treatment, history of chronic renal failure and lack of renal adjustment. In patients with concern for Cefepime neurotoxicity, we recommend monitoring of Cefepime trough levels and renal-dose adjustment. We also further recommend an EEG if there is concern for epileptic

activity with expected EEG findings would be diffuse background slowing and atypical triphasic waves.

Competing Interests

The Authors have no financial or non-financial competing interests to disclose.

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