Continuous Epileptiform Discharges in Patients Treated With Cefepime or Meropenem

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Objective: To test the hypothesis that treatment with cefepime hydrochloride leads to higher incidence of periodic epileptiform discharges compared with treatment with other β-lactams.

Design: Data from hospital pharmacy databases of patients treated with cefepime or meropenem during a 42-month period (from January 1, 2007, through June 30, 2010) were retrospectively crossed with data from the electroencephalography database for the same period.

Setting: Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium.

Patients: Patients who underwent electroencephalographic testing while taking cefepime or meropenem were selected. Only electroencephalographic tests performed during the antibiotic treatment period were considered. Matches were compared with nurses’ medication records to ensure that the antibiotic considered was effectively given.

Main Outcome Measure: Proportions of patients with continuous epileptiform discharges in the 2 groups were compared using the Fisher exact test.

Results: A total of 1120 patients were treated with cefepime and 1572 patients with meropenem. Electroencephalographic testing was performed during treatment in 59 patients treated with cefepime and 80 treated with meropenem (5.26% vs 5.08%, P = .85). Continuous epileptiform discharges were present in 14 patients in the cefepime group and 3 in the meropenem group (1.25% vs 0.19%, P < .001). Blood creatinine concentration was elevated in 5 of the 17 patients (range, 1.5-4.2 mg/dL; reference range, 0.7-1.2 mg/dL), and liver enzyme levels were elevated in 5 patients. No patient had major electrolyte disturbances.

Conclusions: Our study showed a prevalence of electroencephalographic test results with continuous epileptiform discharges in 14 of 1120 patients receiving cefepime (1.25%) but only 3 of 1572 patients receiving meropenem (0.19%). Contrary to the results of previous case series, these electroencephalographic patterns occurred, in most cases, in patients with normal renal function. These results suggest that cefepime may be an independent risk factor for periodic epileptiform discharges, which are associated with worse outcomes. This finding could provide a partial explanation for the higher mortality rates reported in patients treated with cefepime compared with other β-lactams.

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Cefepime hydrochloride and meropenem are broad-spectrum antibiotics that are often selected for empirical monotherapy of febrile neutropenia or other hospital-acquired infections. A study has suggested that the mortality rate may be greater in patients treated with cefepime than in those treated with other β-lactams, giving no obvious explanation for these findings. However, several reports of nonconvulsive status epilepticus (NCSE) occurring in patients with renal dysfunction who were treated with cefepime suggest that neurologic complications may be involved. We compared the proportion of patients who had experienced continuous epileptiform discharges while being treated with cefepime with that of patients who experienced those discharges while being treated with meropenem to determine whether continuous epileptiform discharges were more frequent with cefepime and potentially could provide a partial explanation for the higher mortality rates reported in the literature in these patients.

Methods

Information from the databases pertaining to patients treated with cefepime or meropenem during a 42-month period, from January 1, 2007, through June 30, 2010, was retrospectively crossed with information from the electroencephalographic database (Shell 2000 and Shell+, OSG BVBA, Rumst, Belgium) for the same period. Patients who had undergone electroencephalographic testing while taking cefepime or meropenem were selected. Only the results of electroencephalographic tests performed during the antibiotic treatment period were considered. Matches were compared with nurses’ medication records to ensure that the antibiotic considered was effectively given.
formed during the antibiotic treatment period were considered. Matches were compared with nurses’ medication records to be certain that the antibiotic considered was effectively given. Ictal or possibly ictal electroencephalographic patterns were defined as any electroencephalographic pattern containing continuous epileptiform discharges (generalized periodic epileptiform discharges [GPEDs], periodic lateralized epileptiform discharges, or continuous multifocal spikes) or well-defined epileptic seizures. Most of the electroencephalographic tests were performed intermittently, in 30-minute monitorings using 21 scalp electrodes placed according to the classic 10-20 International System of Electrode Placement. Five of the 14 patients in the cefepime group and 2 of the 3 patients in the meropenem group underwent continuous video electroencephalographic testing performed with a portable machine (Brainlab and BrainRT, OSG BVBA). Proportions of patients with continuous epileptiform discharges in the 2 groups were compared using the Fisher exact test.

**RESULTS**

During the study period, 1120 patients were treated with cefepime and 1572 patients with meropenem. The electroencephalographic tests were performed during treatment in 59 patients treated with cefepime and in 80 of those treated with meropenem (5.26% vs 5.08%, P = .85). Death rates were identical in the cefepime and meropenem groups (21 of 59 [35.6%] vs 29 of 80 [36.2%]). In the cefepime group, the electroencephalographic indications were altered consciousness (n = 9), suspicion of seizures (n = 3), suspicion of postanoxic coma (n = 1), and unknown (n = 1). In the meropenem group, the electroencephalographic indications were suspicion of seizures (n = 2) and cranial trauma (n = 1).

Continuous epileptiform discharges were present in 14 patients in the cefepime group and 3 in the meropenem group (1.25% vs 0.19%, P < .001). The characteristics of these patients are presented in the Table. Blood creatinine concentration was elevated in 5 of the 17 patients (range, 1.5-4.2 mg/dL; reference range, 0.7-1.2 mg/dL; to convert to micromoles per liter, multiply by 88.4), and liver enzyme levels were elevated in 5 patients. No patient had major electrolyte disturbances. Mean time to diagnosis of suspected NCSE was 5 days (range, 1-10 days) after antibiotic treatment was started. The 30-day mortality rate was 42.8%.

In the cefepime group, the continuous epileptiform discharges were characterized as continuous GPEDs without morphologic variation (n = 5), continuous GPEDs with morphologic variation (n = 1), continuous GPEDs with spreading and morphologic variation (n = 1), intermittent GPEDs with spreading and morphologic variation (n = 3), intermittent GPEDs on stimulus (n = 1), and intermittent GPEDs on probable awakening (n = 1). Two patients experienced monomorphic intermittent GPEDs. Half of the patients were treated for those periodic epileptiform discharges (PEDs). Six patients improved, 3 with various combinations of antiepileptic drugs associated with antibiotic treatment discontinuation (2 fortuitously) and 3 with only change in antibiotic used. Of the 6 patients who improved with cefepime treatment discontinuation, 3 underwent electroencephalographic testing in the following days that revealed disappearance of the GPEDs. One patient was treated with a combination of antiepileptic drugs but died.

The mean age of the patients was 67 years. Ten patients had extracerebral infectious sepsis and 4 had febrile neutropenia. No patient had a history of epilepsy; only 1 patient had been treated with valproic acid for an episode of clonic movements occurring during severe bradyarrhythmia. The results of brain imaging showed that 1 patient had a 10-mm chronic subdural hematoma, 1 had sequelae of a left frontal stroke, 1 had possible left cerebellar metastases, and 1 had nonspecific leukoencephalopathy.

In the meropenem group, all patients had GPEDs with morphologic variations and spreading, 2 continuous and 1 intermittent. Two patients were treated with antiepileptic drugs, which improved the electroencephalographic pattern, but 1 of those patients died. One patient had posttraumatic bilateral frontal lesions and the others had normal brain tomodensitometric results. An example of electroencephalographic test results (those for patient 1) is shown in the **Figure**.

**COMMENT**

Meropenem and cefepime are used for severe intrahospital infections, and all patients in both groups had severe infections. Periodic electroencephalographic patterns were 5-fold more frequent in the cefepime group than in the meropenem group, suggesting that cefepime may be associated with a greater risk of brain toxicity (ie, direct toxicity and/or NCSE) than meropenem. It might have been possible that the physicians in charge were more aware of possible brain toxicity in patients receiving cefepime than in those receiving meropenem, thus artificially increasing the number of electroencephalographic tests ordered in the cefepime group. Because the number of patients who underwent electroencephalographic testing was similar in both groups, we do not believe that this higher occurrence of PEDs in patients treated with cefepime could be attributed to increased clinical suspicion of seizures. We also do not believe that a worse clinical state could explain the differences because the 30-day mortality was identical in the 2 treatment groups. Furthermore, of the 6 treated patients who had improved, all discontinued cefepime treatment. Changing of the antibiotic used was the sole treatment in 3 of them because cefepime neurologic toxicity was suspected. Those clinical improvements strongly favor a causative role of cefepime in the epileptiform episodes.

Clinical findings are limited in a comatose patient, and the electroencephalographic test results can be misleading, especially when a status epilepticus lasts for several days. For instance, the rate of NCSE in patients with an unexplained decreased level of consciousness is reported to be as high as 8% to 18%. Patients with central nervous system disease, such as intracerebral hemorrhage, brain infection, brain tumors, head trauma, or subarachnoid hemorrhage, are most likely to develop NCSE. With continuous electroencephalographic monitoring, as many as 34% of patients in neurologic intensive care units have nonconvulsive seizures, and three-fourths of them have NCSE. In medical intensive care units, in pa-
The diagnostic distinction of NCSE from electrographic seizures is challenging in critically ill patients. Recently, a new term has been coined to group these conditions into a single entity: clinically unrecognized electrographic seizures (CLUES). Increasing evidence shows that CLUES bear a worse prognosis. In a recent retrospective study by Oddo et al, regarding the prevalence of electrographic seizures and PEDs in patients with sepsis in a medical intensive care unit, electrographic seizures and PEDs were found in 9% and 16%, respectively, of patients who underwent continuous electroencephalographic monitoring. Most of those PEDs were GPEDs. The GPEDs we report in our patients could be due to sepsis. However, this study did not consider antibiotic treatment as a coexisting cause of those PEDs. The important difference we found in the prevalence of GPEDs between cefepime and meropenem points to a role of some antibiotics in the association described between PEDs and sepsis. Another argument for a causative role of cefepime in our series is the disappearance of GPEDs on the results of the electroencephalographic tests made after cefepime treatment discontinuation in 3 of the 6 patients whose conditions improved and who underwent electroencephalographic testing.

β-Lactams are known to induce seizures, and high concentrations of cephalosporins in the brain or cerebrospinal fluid (CSF) are epileptogenic by competitive antagonism of inhibitory neurotransmitter γ-aminobutyric acid in a dose-dependent mechanism. In healthy individuals, this cephalosporin concentration is kept low by the low permeability of the blood-brain barrier and by its active transportation from CSF to blood. In renal failure, the accumulation of toxic organic acids competes with...
cefepime for active transportation from CSF to blood and, therefore, it increases cefepime concentrations in the CSF. This was an explanation offered in 2 small series reporting NCSE in patients with renal impairment who were treated with cefepime. So far, only 1 report has been published of NCSE in a patient with normal renal function (blood creatinine concentration, 1.2 mg/dL). The finding of normal-range blood creatinine concentrations in 64.3% of our patients with PEDs was, therefore, unexpected. Predisposing brain lesions cannot explain our observations because only 2 patients had abnormal focal brain imaging.

A high occurrence of PEDs in patients with normal renal function treated with cefepime has not been reported previously, to our knowledge. In our series, most of the patients were critically ill. In these patients, an increase in blood-brain barrier permeability influenced by an inflammatory response may have allowed the accumulation of cefepime in the brain or the CSF and thereby facilitated the development of PEDs. Diagnosis of CLUES can only be made by observing the results of electroencephalographic testing; the fact that patients who are treated with cefepime but have normal renal function are not considered at risk of developing periodic epileptiform discharges may explain why this has not been reported previously.

Continuous PEDs observed via electroencephalographic test results, such as GPEDs, are not specific for NCSE. The differential diagnosis of such discharges is broad and includes diffuse metabolic or toxic encephalopathy and rare diseases, such as Creutzfeldt-Jakob disease. This pattern also is commonly seen in postanoxic coma, in which it is associated with a poor prognosis if present more than 24 hours after resuscitation. In our study population, no patient had metabolic failure likely to cause a periodic pattern on the electroencephalographic test results. One patient had postanoxic coma but underwent an electroencephalographic test before cefepime was started, the results of which did not show GPEDs; also, no patient had a history compatible with Creutzfeldt-Jakob disease. The periodic pattern could, therefore, be considered indicative of CLUES whether due to septic encephalopathy, a direct toxic effect of the drug, or a combination of both. CLUES are associated with a worse prognosis, so the higher prevalence of PEDs in our cefepime group could explain partly the higher mortality rate reported with cefepime than with other β-lactams.

One major limitation of this study is its retrospective design. The electroencephalographic tests were ordered mostly for altered consciousness and then to exclude seizures. We cannot be certain that an electroencephalographic test was performed in all patients who received cefepime or meropenem and had altered consciousness. Our results probably underestimate the proportion of PEDs in both groups because most patients underwent routine instead of continuous electroencephalographic testing: studies of the latter in critically ill patients show that it reveals seizure activity in 19% of patients, but routine electroencephalographic testing misses most of them. Yet, it is often not structurally possible to perform continuous electroencephalographic testing in all patients with sepsis, but we think that in such patients with altered consciousness, especially if they are being treated with cefepime, continuous electroencephalographic test-
ing should be performed or a change of antibiotic should be considered.

Our study showed a prevalence of electroencephalographic test results showing continuous epileptiform discharges in 14 of 1120 patients receiving cefepime (1.25%) but in only 3 of 1572 (0.19%) patients receiving meropenem. Contrary to the findings of previous case series, these electroencephalographic patterns occurred, in most cases, in patients with normal renal function. No obvious explanation can be given other than the influence of cefepime for the development of PEDs because brain lesions or central nervous system disease were found in only a few cases. The PEDs observed via electroencephalographic testing, such as GPEDs, are not specific; however, causes other than antibiotics were as likely to occur in the meropenem group as in the cefepime group. These results suggest that cefepime may be an independent risk factor for PEDs. This hypothesis should be confirmed in a prospective study. In the meantime, we recommend that electroencephalographic testing (or continuous electroencephalographic monitoring, if available) should be performed in patients with unexplained altered consciousness who are receiving treatment with cefepime or that a change of antibiotic should be considered.

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