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The neurotoxicity and safety of treatment with cefepime in patients with renal failure

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Abstract

Background: Cases of cefepime neurotoxicity have been Sporadically reported in patients with renal failure. The neurotoxicity of cefepime might be underestimated and the frequency of its neurotoxic effects may be insufficiently recognized.
Methods: We retrospectively reviewed the files of patients with renal failure who were treated with cefepime and who developed neurological complications.
Results: All 8 patients developed decreased conscience, confusion, agitation, global aphasia, myoclonus, chorea-athetosis, convulsions and coma. The latency, the period between the start of treatment and neurologicaldeterioration, was $4,75 \pm 2,55$ days (range: 1–10 days). All patients died $17 \pm 14,7$ days (range: 1–42 days) after becoming symptomatic. Three of them died shortly after neurological deterioration. Five patients developed a neurological "tableau" with global aphasia. Three patients showed clinical improvement after the discontinuation of cefepime. Electroencephalography revealed diffuse slow-wave activity (delta) and triphasic sharp wave activity. These findings confirm the possible neurotoxicity of treatment with cefepime in patients with renal failure. In none of the deceased patients have we been able to directly demonstrate a causal relationship between neurotoxicity and mortality. However, when a patient treated with cefepime develops neurological deterioration or aphasia, one must be aware of cefepime's potential neurotoxicity and treatment should be stopped.
Conclusion: We recommend that, in view of the high and unexplained mortality, the use of cefepime in patients with kidney failure should be carefully considered.

Keywords: cefepime; neurotoxicity; renal failure; kidney disease

Introduction

Cefepime is a fourth-generation cephalosporin active against both gram-positive and gram-negative organisms.

It is administered parenterally for the treatment of severe infections [1]. Approximately 85% of the drug is excreted unchanged by the kidneys. Renal clearance of cefepime diminishes proportionally with a decrease in the glomerular filtration ratio (GFR). The half-life of cefepime in patients with renal failure and a creatinine clearance <10 ml/min is approximately five times longer compared to individuals with normal renal function [2], necessitating dosage adjustment in patients with renal impairment.

The epileptogenic side effect of beta-lactam (ß-lactam) antibiotics was first described in 1945 [3]. The exact mechanism involved in the neurotoxicity has not been clarified yet. Neurotoxicity in patients with renal failure and treated with cefepime has been reported sporadically.

In the present report, we reviewed the files of eight patients with renal impairment who developed neurotoxicity with lethal outcome after treatment with cefepime for severe infections.

Methods

The files of eight patients, admitted to our hospital between June 1999 and October 2006, who suffered from renal insufficiency and who developed neurological symptoms during treatment with cefepime were reviewed.

In each patient, the indication for treatment and the dosages of cefepime administration were established. These dosages were compared with the dosages and dosing intervals for patients with impaired renal function as recommended by the supplier and the Sanford Guide to Antimicrobial Therapy 2005–2006 [4,5]. Renal function was calculated following the Cockroft–Gault equation when appropriate.

The clinical findings during neurological deterioration and the latency, the period between the start of cefepime treatment and neurological deterioration, were noted.

To exclude other reasons for the neurological alterations, all laboratory findings were evaluated. We paid special attention to the glycaemia, electrolyte and metabolic disturbances, signs of infection and arterial blood gas results. We also searched for evidence of stroke.

The administered medication was evaluated for potential neurotoxic effects and epileptogenic adverse effects.

The results of all technical examinations were evaluated. We collected the results of the patients who had undergone computed tomography (CT) of the brain, electroencephalography (EEG) and lumbar puncture. These findings were correlated with the clinical findings.

We searched for potential treatment changes before or during cefepime administration and for the outcome after patients became symptomatic.

Means have been calculated with standard deviation and range.

Results

During the 7-year period, we identified eight patients with cefepime neurotoxicity (Table 1). This group consisted of five men and three women with a mean age of 69.5 ± 11.7 years (range: 49–84 years).

Comorbidity

All patients had renal impairment. Five patients (B, D, E, F and H) had end-stage kidney disease (creatinine clearance <15 ml/min) and were treated with chronic haemodialysis. Two patients had previous kidney transplantation. Patient G had undergone renal transplantation 4 years before admission. He presented acute on chronic renal insufficiency necessitating intermittent haemodialysis. Another transplant patient (C) had a creatinine clearance of 17 ml/min due to relapse of focal segmental glomerulosclerosis in a kidney transplant. During her hospital stay, her renal function deteriorated as a result of a traumatic retro-peritoneal bleeding and haemodialysis was started. Patient A had a creatinine clearance of 50 ml/min and had undergone one haemodialysis session after an acute on chronic renal insufficiency.

Indication

Three patients (A, E and G) were treated with cefepime for sepsis with *Pseudomonas aeruginosa*. Two patients (B and C) received cefepime empirically for a serious infection. Patient D suffered from a serious infectious COPD exacerbation. Patient F was treated with cefepime for pneumonia. Patient H was treated for febrile neutropenia.

Dose

The administered dose of cefepime varied. This is due to the changing of the dosing instructions by the supplier following a 'dear doctor' letter sent in November 2000. The last patient (H) received a dose and dosing interval adapted to the degree of renal impairment, as proposed by the manufacturer.

Symptoms

The neurological symptoms varied and were slowly progressive. They consisted of decreased conscience, confusion, agitation, global aphasia, myoclonus, choreaathetosis, convulsions and coma. Four patients (B, E, F and G) had global aphasia during neurological deterioration.

Timing and latency

The latency, the period between the start of cefepime treatment and neurological deterioration, was 4.75 ± 2.55 days (range: 1–10 days). The patients died 21.8 ± 15.5 days (range: 6–48) after starting cefepime and 17 ± 14.8 days (range: 1–42) after the first neurological symptoms were recorded. Treatment with cefepime was discontinued in every patient 2.4 days (range: 0–12 days) after the first neurological symptoms had been observed. An average of 14.6 days (range: 1–42 days) went by between discontinuation of cefepime and death.

Five patients survived for a longer period. Patients F, G and H had clinical improvement after stopping cefepime, but patients F and G again had progressive neurological deterioration. Patient F became symptomatic after 3 days of treatment with cefepime. Cefepime was temporarily stopped resulting in clinical improvement. He became more conscious and communicative again. Because of relapse of fever, treatment with cefepime was restarted. During this treatment, he developed persistent decreased conscience. Thereafter, he developed aphasia and evolution to coma before death. At first, patient G presented motoric aphasia with normal conscience. He showed slight neurological improvement after the discontinuation of cefepime, but then developed global aphasia and decreased conscience before dying. The mental condition of patient H improved after cefepime had been stopped the day after the first symptoms developed. Nevertheless, she died 42 days after stopping cefepime.

Further investigations

Patients A, C and D died within 2 days after stopping the cepime treatment. There was not enough time to observe neurological improvement and to perform more examinations.

Patients B, E, F, G and H underwent further investigations. An EEG revealed diffuse slow-wave activity (delta) and triphasic sharp wave activity suggesting a metabolic-toxic disturbance. There was no epileptiform activity (Figure 1). In one patient (G), we recorded improvement on EEG recordings after the discontinuation of cefepime.

Four patients had undergone a CT scan of the brain. In patient B, there was evidence of bilateral parieto-occipital and basal ganglia ischaemic stroke. Nevertheless, the timing suggests cefepime toxicity. Patient H had improved white matter lesions on a control MRI scan of the brain compared to previous imaging.

All patients had renal impairment and showed elevated inflammatory laboratory parameters. They all had renal insufficiency before starting cefepime or were already under haemodialysis treatment. There is no evidence that uraemia per se was responsible for the neurological symptoms.

The results of laboratory investigations or arterial blood gas analysis are not contributive.

The lumbar puncture of patient F was normal. Lumbar puncture in patient H revealed a slightly elevated lactate of 1.8 μmol/l (normal range <1.7 μmol/l) with a normal total protein, glucose and cytology and microbiological analysis.

Table 1. Patient characteristics of eight patients with cefepime-induced neurotoxicity

Patient	Age, gender	Comorbidity	Indication	Dose	Latency (days)	Symptoms	EEG	Time between start of symptoms and death (days)
A	74, M	CKD	Sepsis	35 g/7 days	7	Coma, myoclonus	No	1
B	73, M	ESRD	Empiric	16 g/4 days	1	Agitation, aphasia	Yes	18
C	49, F	CKD[a]	Empiric	7 g/4 days	4	Agitation, confusion	No	2
D	71, M	ESRD	COPD-exacerbation	44 g/5 days	4	Coma, myoclonus	No	2
E	82, F	ESRD	Sepsis	7 g/6 days	4	Aphasia, myoclonus, chorea-athetosis, convulsions, coma	Yes	10
F	84, M	ESRD	Bilateral pneumonia	20 g/6 days and 13 g/10 days	3	Aphasia, myoclonus, hyperexcitability	Yes	31
G	53, M	CKD[a]	Sepsis	63 g/11 days	10	Aphasia, coma	Yes	30
H	70, F	ESRD	Febrile neutropenia	6 g/6 days	5	Myoclonus, coma	Yes	42

[a]Renal transplantation, CKD = chronic kidney disease.
M = male, F = female, ESRD = end-stage renal disease.

Fig. 1. EEG recordings of patient E. The EEG recordings revealed diffuse slow-wave activity (delta) and triphasic sharp wave activity, suggesting a metabolic-toxic disturbance. There was no epileptiform activity. This pattern was found in each patient.

The administered medication was evaluated for potential neurotoxic effects and adverse epileptogenic effects. It is highly unlikely that other drugs taken by the patients such as tacrolimus or epoietin may have induced the neurological tableau, since these medications had already been used for a long time and were well tolerated.

Autopsy of patient F suggests that he died of cardio-respiratory failure due to severe atherosclerosis and emphysematous-anthracosilicotic lung disease with tracheitis, bronchitis and bronchopneumonia. The findings in patient G suggest that he died of myocardial infarction with heart failure and pulmonary oedema. He also suffered from bilateral pneumonia on autopsy. Autopsy of patient H suggests that she died of *E. coli* pneumonia.

Patient A died after ventricular tachycardia and unsuccessful CPR. Patient B died shortly after starting comfort care. Patient C died after cardio-respiratory arrest. The cause of death of patients D and E is unclear.

Discussion

Several cases of cefepime neurotoxicity have been reported [6–16]. Around 3% of the patients treated with cefepime are said to have experienced adverse central nervous system effects [17]. Nevertheless, different publications cast doubt upon this low prevalence [7,11,12,13]. In the current publication, we report eight cases of patients with renal

impairment, who were treated with cefepime and developed a metabolic-toxic encephalopathy. All patients subsequently died.

The latency, the period between the start of cefepime treatment and neurological deterioration, was 4.75 ± 2.55 days (range: 1–10 days). This latency corresponds to the latency described in previous publications [6–16]. The neurological symptoms consisted of decreased conscience, confusion, agitation, global aphasia, myoclonus, chorea-athetosis, convulsions and coma. Three patients died shortly after the first symptoms had developed. Four deceased patients developed a neurological tableau with global aphasia. EEG revealed diffuse slow-wave activity (delta) and triphasic sharp wave activity. There was no epileptic activity (Figure 1).

These findings correspond to a metabolic-toxic encephalopathy induced by cefepime. We have not identified other responsible factors in these critically ill patients under polypharmacy. The obvious time relationship between the start of therapy, the clinical-neurological improvement after the discontinuation of cefepime and the improvement of the EEG recordings in one patient are highly suggestive of cefepime toxicity. One patient deteriorated again after having restarted the treatment with cefepime, indicating cefepime toxicity.

A wide range of possible neurotoxic complications after cefepime administration has been described: confusion, disorientation, hallucinations, agitation, myoclonus, convulsions, non-convulsive status epilepticus and coma [6–16]. Convulsions and non-convulsive status epilepticus are the most frequently described adverse neurological effects. In our population, the aphasia during the neurological deterioration is striking.

The exact mechanism involved in neurotoxicity has not been clarified yet. In 1945, the epileptogenic effect of ß-lactam antibiotics was first described in laboratory animals with renal impairment [3]. Competitive antagonism with the principal inhibitory neurotransmitter GABA is believed to be responsible for neuronal hyperexcitability [18,19]. In the case of renal insufficiency, the concentration of cefepime in the spinal fluid is said to rise due to competitive inhibition of the active transport from cerebrospinal fluid to blood by accumulation of toxic organic acids, higher blood–brain barrier permeability and low-serum protein binding. All our patients had renal insufficiency and were being treated with relatively high doses of cefepime for serious infections. Six patients were treated in the period from 1999 till 2001. During this period, most adverse neurotoxic effects of cefepime were published and attention was paid to dose reduction for the first time. Inappropriate dosing does not explain the adverse events since non-convulsive status epilepticus has been reported in a patient with normal renal function and with adequately adapted therapeutical cefepime doses [15]. In the current publication, one patient also died after administration of a correct dose and correct dosing intervals.

Cefepime is predominantly excreted by renal clearance and around 85% of the drug is excreted unchanged by the kidneys. The half-life of cefepime in patients with renal failure and creatinine clearance <10 ml/min is approximately five times longer compared to patients with normal renal function and increases from around 2.3 to 13.5 and even 22 h [2,20]. In patients with end-stage renal disease treated with haemodialysis, elimination is determined by the characteristics of the dialysis membrane. The half-life of cefepime during dialysis can vary between 1.6 and 2.3 h depending on the use of high- or low-flux membranes. In practice, factors such as blood and dialysate flow also determine the characteristics of dialysis. Thus, cefepime pharmacokinetics are difficult to predict in patients with severe renal insufficiency [1,2,20].

The prognosis for patients with adverse neurological effects varies. In previous reports, recovery, with or without haemodialysis, seems to depend on an early diagnosis, subject to the degree of awareness of the potential adverse effects of cefepime. Severe infection and high comorbidity, polypharmacy, advanced age of the patients, the low specificity of the clinical presentation and the low index of suspicion hamper the diagnosis. Neurological deterioration is often attributed to the infectious pathology or comorbidity and adverse effects of medication are underestimated. Previous publications also point to unawareness and subsequent delayed diagnosis of neurotoxicity [12,13]. Several studies suggest that partial or complete recovery follows an early diagnosis and withdrawal of cefepime [7,9,10,12,13]. In the current population, treatment with cefepime was discontinued on average 2.4 days (range: 0–12 days) after the first neurological symptoms were observed. In spite of an early diagnosis and discontinuation, each patient died. In none of the deceased patients, we demonstrated a direct causal relationship between neurotoxicity and mortality. Nevertheless, an indirect relationship is possible.

Several studies on the efficiency and safety of cefepime do not mention adverse effects compromising the use of cefepime [21,17,22]. In these studies, overall mortality rates amount to 1%, suggesting that the inclusion criteria must have excluded patients with serious infection or comorbidity. Mortality of patients with renal insufficiency treated in an intensive care setting is around 15% and rises to 25% when dialysis is necessary [23,24]. Mortality due to sepsis in intensive care varies between 20% and over 50% [25]. As most of the cases of cefepime neurotoxicity were reported in patients with renal impairment, it seems advisable to apply prospective pharmacovigilance in this population at risk. The high mortality in our series remains unexplained. In a recent published meta-analysis comparing different antibiotic regimens for febrile neutropenia, use of cefepime was associated with higher all-cause mortality at 30 days than other ß-lactams (RR 1.44, 95% CI 1.06–1.94, 3123 participants) [26].

In conclusion, our findings confirm the adverse neurotoxic effects of cefepime treatment for a serious infection in patients with renal insufficiency. Our data also suggest that the neurotoxic adverse effects are underestimated.

In view of the high and unexplained mortality in our patients and the finding of an increased mortality in comparison with other antibiotics following treatment with cefepime [26], we recommend that cefepime should be used with caution and that studies in patients with kidney disease should be performed before recommending a more general use.

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