ischiatic pressure sore. No other comorbidities were present. Culture of the ulcer biopsy specimens grew methicillin-resistant Staphylococcus aureus, multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. The patient started antibiotic treatment with 15 mg/kg amikacin daily intravenously and 100 mg of tigecycline intravenously, as initial dose, followed by 50 mg twice daily as a maintenance dose. The renal and liver functions were normal. The patient initially tolerated the antibiotics without complaint of nausea and vomiting or other adverse effects. During the second week of antibiotic therapy, the patient underwent surgery including ulcerectomy, partial ischiectomy, and coverage with the gluteal muscle flap and V-Y advancement flap. On the first post-operative day, the patient suddenly developed nausea, vomiting and acute severe upper abdominal pain. Blood tests showed increased amylase (312 U/L), lipase (382 U/L), white blood cells (42 770/μL) and C-reactive protein (131 mg/L). The abdominal CT scan showed inflammation of the pancreas and peripancreatic fat, necrosis of 40% of the pancreatic gland, peripancreatic stranding, and fluid collection (Balthazar CT severity index 7). No other common causes of acute pancreatitis, such as alcoholism, stones, total parenteral nutrition, endoscopic retrograde cholangiopancreatography, trauma, hypertriglyceridaemia and hypercalcemia, were identified. Drug-induced pancreatitis was suspected and tigecycline immediately discontinued. Owing to the critical condition (APACHE II score 14), the patient was treated in the intensive care unit with aggressive fluid resuscitation, pain management, proton-pump inhibitors, total parenteral nutrition and antimicrobial prophylaxis with imipenem/cilastatin. The symptoms resolved and pancreatic enzymes normalized within 10 days. Interestingly, the patient developed acute necrotizing pancreatitis on day 12 of tigecycline treatment and 8 h after receiving a single dose of propofol for the induction of general anaesthesia. Propofol was the only other medication in the patient’s regimen that could possibly induce pancreatitis. Cases of propofol-related pancreatitis, even after a single dose, have been reported. In some cases, propofol has been implicated in causing pancreatitis by increasing the level of triglycerides. However, the pathogenesis is unknown and the causal relationship remains to be established. In our patient, the level of triglycerides remained normal; moreover, the patient had received propofol on two previous occasions for general anaesthesia without developing pancreatitis. It is possible that propofol could have a role as a cofactor triggering acute pancreatitis in a previously tigecycline-sensitized pancreas. The concomitant administration of tigecycline and propofol led to the more severe pancreatic injury observed in this case.

The reported mortality rates of <1% in patients with interstitial pancreatitis dramatically increase to 10%–23% in patients with necrotizing pancreatitis. Clinicians should be aware of this potentially life-threatening side effect of tigecycline. Close monitoring of gastrointestinal symptoms and serum amylase, especially after the first week of treatment, have been advocated previously.

Based on our experience presented herein, we suggest that special caution should be exercised when administering tigecycline in association with propofol.

The patient gave informed consent to the publication of this article.

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**Transparency declarations**

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**References**


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**Blood and CSF monitoring of cefepime-induced neurotoxicity: nine case reports**

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**Keywords:** trough concentrations, CSF concentrations, renal failure

Sir, Cefepime is a parenteral fourth-generation cephalosporin commonly used as a first-line empirical treatment for severe...
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>CLCr at the time of the neurological symptoms, mL/min</th>
<th>Renal status</th>
<th>Duration of cefepime treatment at the time of the neurological effects</th>
<th>Clinical features</th>
<th>Treatment</th>
<th>Clinical outcome after cefepime withdrawal</th>
<th>Cefepime dose</th>
<th>Cefepime levels, mg/L (time after last administration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>27, 10 and then 7.05</td>
<td>oligo-anuric AKD</td>
<td>5 days</td>
<td>altered level of consciousness</td>
<td>4 HD sessions</td>
<td>recovery</td>
<td>2 g daily (for 3 days), 1 g daily (thereafter)</td>
<td>48.1 (8 h); 1.1 (after 4 HD sessions)</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
<td>15 (previously 36)</td>
<td>previous episodes of AKD with piperacillin and amikacin</td>
<td>3 weeks</td>
<td>convulsions and altered level of consciousness</td>
<td>clonazepam + additional HD</td>
<td>recovery</td>
<td>4 g twice daily</td>
<td>160 (20 h); 29 (32 h); 7 (92 h)</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>9</td>
<td>ESRD on HD</td>
<td>4 days</td>
<td>mental confusion</td>
<td>additional HD</td>
<td>recovery</td>
<td>1 g/48 h (after dialysis)</td>
<td>73 (48 h)</td>
</tr>
<tr>
<td>4</td>
<td>84</td>
<td>&lt;20</td>
<td>CKD</td>
<td>6 days</td>
<td>somnolence after withdrawal of hypnotics, and clonic movements</td>
<td>additional HD</td>
<td>recovery</td>
<td>2 g daily</td>
<td>74 (12 h)</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>12 (MDRD)</td>
<td>ESRD on HD</td>
<td>3 days</td>
<td>confusion, somnolence</td>
<td>additional HD</td>
<td>recovery</td>
<td>2 g three times a day for 2 days then 2 g twice daily</td>
<td>37.6 (after dialysis); &lt;0.5 (72 h)</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>20</td>
<td>CKD</td>
<td>2 days</td>
<td>visual hallucinations and confusion</td>
<td>recovery</td>
<td>1 g daily</td>
<td>67.2 (24 h); &lt;0.5 (168 h)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>77</td>
<td>15 (previously 20)</td>
<td>CKD</td>
<td>54 h</td>
<td>clonic movements and confusion</td>
<td>clonazepam</td>
<td>death from other causes</td>
<td>3 g daily</td>
<td>41 (31 h); 4 (79 h)</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>NA</td>
<td>anuric AKD</td>
<td>NA</td>
<td>status epilepticus</td>
<td>death from other causes</td>
<td>2 g twice daily in combination with amoxicillin/clavulanic acid</td>
<td>224 (12 h)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>14</td>
<td>CKD</td>
<td>NA</td>
<td>day 2: confusion; day 6: status epilepticus</td>
<td>recovery</td>
<td>500 mg/day then 2 g daily</td>
<td>60 (24 h)</td>
<td></td>
</tr>
</tbody>
</table>

AKD, acute kidney disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; HD, haemodialysis; NA, not available.
infections such as pneumonia or septicemia, especially in neutropenic patients. Neurotoxicity is a well-known adverse effect of cephalosporins and, for cefepime, has been mainly reported in patients treated with high dosages with renal failure. Cefepime-related neurotoxicity reportedly affects 3% of treated patients, although this may be an underestimate.1

Over the last 2 years, six cases of cefepime neurotoxicity were documented in our hospital by demonstration of excessive drug concentrations. Here, we describe these six cases and discuss three cases we have previously published.2,3 Biological fluid assays of cefepime were performed by HPLC for the nine patients with suspected neurological events. The patients’ characteristics are described in Table 1. In all patients, cefepime overdosage was confirmed by analysis of cefepime blood concentrations.

After withdrawal of cefepime, the patients' neurological status improved in all cases. In case 3, cefepime treatment was continued after dose adjustment. In five cases, a decrease in cefepime concentration was observed during neurological improvement. All patients had chronic kidney disease (CKD) or acute kidney disease. Four patients with CKD underwent supplementary dialysis sessions in order to decrease the cefepime concentrations. CSF was available for two patients; measurement of cefepime concentrations in CSF confirmed brain accumulation.

The proconvulsive action of cephalosporins may be related to a suppressive effect on inhibitory neurotransmission. Sugimoto et al.4 have suggested that β-lactam antibiotics may induce convulsions via a concentration-dependent inhibition of GABA_A- mediated neurotransmission, leading to a decrease in seizure threshold. This hypothesis is supported by the observation that benzodiazepines were effective in treating convulsions in most reported cases of cephalosporin neurotoxicity (including cases 2 and 7 in our series). Other mechanisms involving tumour necrosis factor-α or enhanced glutaminergic activity have also been suggested.1

Cefepime is mostly eliminated unchanged via glomerular filtration, and its renal clearance is closely related to CL_cr.5 This justifies dose adjustment according to renal function. However, in patients with renal disease, CSF cefepime concentrations may also be increased in relation to increased blood–brain barrier permeability, with decreased serum protein binding and accumulation of organic acids leading to competitive inhibition of active transport from CSF to blood.5 Thus, when CSF is available, determination of cefepime concentration may be of clinical value. The CSF/blood ratio is usually around 10%.1 In cases 2 and 7 in our series, this ratio was increased to 45% and 34%. In case 2, the latency of the adverse effect was longer than that usually described. It can be hypothesized that renal failure deteriorated slowly, resulting in progressive cefepime accumulation until toxic levels were reached.

As with most cases published in the literature, the cases reported here concern patients treated with high drug dosages with renal failure, especially true in cases 2, 5, 7 and 8 where the doses used, in order to treat severe infections, were too high in terms of renal function. However, cefepime-induced neurotoxicity has also been reported after dose adjustment to renal function (according to the Summary of Product Characteristics).2 Lastly, some cases have also been described in patients who developed acute renal failure (in response to concomitant treatments or clinical events) during cefepime treatment (as in cases 2 and 8 of the present series).

When overdosage is suspected, cefepime treatment should be discontinued, as, in this series and in most published cases, discontinuation of cefepime, either alone or associated with anti-epileptic therapy, led to complete resolution of the neurological events. Due to the low drug–protein binding of cefepime, a 3 h haemodialysis session is efficient to remove 70% of a given dose. Many published cases have reported recovery of normal neurological status after haemodialysis.1

Cefepime overdosage may sometimes be difficult to diagnose, since treated patients often present comorbidities that could at least partially account for the neurological symptoms. Thus, monitoring of renal function and cefepime blood concentrations appears to be of value in patients with renal failure, elderly patients and those with a history of neurological disease.

Target trough concentrations of cefepime have not been well established. Lamoth et al.6 have described an association between high trough concentrations and neurological adverse events and predicted that a concentration ≥22 mg/L has a 50% probability of inducing neurotoxicity. The trough concentrations in the present series were all ≥22 mg/L, and clinical improvement was associated with a decrease in blood concentration.

Our series confirms that cefepime accumulation can be associated with neurological adverse effects. Most cases occur in patients with renal failure and sometimes despite dose adjustment for renal function. Monitoring of blood concentration therefore appears to be a useful tool to avoid or confirm cefepime overdosage and to monitor neurological improvement. Determination of CSF cefepime concentrations may also help to confirm the role of cefepime in neurological events.

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**Transparency declarations**
None to declare.

**References**
2. Lemaire-Hurtel AS, Gras-Champel V, Hary L et al. [Recommended dosage adaptation based on renal function is not always sufficient to avoid bêta-lactam antibiotics side effects]. *Nephrol Ther* 2009; 5: 144–8.