

# Therapeutic drug monitoring when using cefepime in continuous renal replacement therapy: seizures associated with cefepime

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Rapid, dynamic changes in organ function are common in the intensive care unit, and are being increasingly understood as a cause of altered drug exposures. Changes in the functionality of the interventions of medical care, such as extracorporeal circuits that are known to affect drug concentrations, can also cause similar effects. In cases of renal replacement therapy (RRT), doses of drugs administered can be several times higher than those necessary in acute renal failure. It follows that drug dosing not adjusted to low RRT efficiency or the clotting of RRT filters will result in high exposures of a drug, and potential toxicities. A challenge for ICU clinicians is the unpredictable efficiency of RRT. This issue has been demonstrated in numerous controlled pharmacokinetic studies, with patients receiving the same dose of a drug and being prescribed the same RRT modality and settings, and having vastly different plasma concentrations of the drug.<sup>1-4</sup>

The likelihood of inappropriately high drug concentrations occurring in some critically ill patients could be considered high. The morbidity associated with potential drug toxicities can also increase health care costs, due to prolonged ICU and hospital lengths of stay. In the presence of such unpredictability, direct measurement of blood concentrations of some drugs, particularly antibiotics like cefepime, may be considered advantageous for minimising potential patient harm. We present a case of an elderly patient receiving RRT who was administered cefepime, and subsequently developed cefepime-induced seizures.

## Clinical record

An 82-year-old man was admitted to the ICU with increasing shortness of breath, a productive cough and atrial fibrillation. His medical history included ischaemic heart disease, chronic renal impairment (with a baseline creatinine level of 170  $\mu\text{mol/L}$ ) and he was an ex-smoker. The chest x-ray taken at admission revealed right upper zone and left lower zone consolidation consistent with bilateral pneumonia.

His white cell count was  $14.6 \times 10^9/\text{mL}$ , neutrophil count  $12.4 \times 10^9/\text{mL}$  with toxic granulation, C-reactive protein level 276 mg/L, creatinine level 292  $\mu\text{mol/L}$  and urea level

## ABSTRACT

Ensuring effective, safe drug dosing in critically ill patients can be difficult, due to variable and dynamic organ function.

An 82-year-old man was admitted to the intensive care unit with severe community-acquired pneumonia, septic shock and progressive organ failure. He required ventilation and continuous renal replacement therapy. He developed seizures which we believe were due to cefepime toxicity. Following the first seizure, we took serial measurements of plasma cefepime levels, and a single measurement of the cerebrospinal fluid (CSF) cefepime level. The peak plasma cefepime concentration was 73.8  $\mu\text{g/mL}$  (minimum inhibitory concentration of target enterobacteriaceae is 8  $\mu\text{g/mL}$ ) and the CSF level was 6.1  $\mu\text{g/mL}$ . The patient had four seizures during the period of high plasma cefepime concentration, but no more episodes once the drug level decreased to non-toxic levels.

This case highlights the difficulty in predicting pharmacokinetics in critically ill patients, particularly those receiving renal replacement therapy. We suggest that therapeutic drug monitoring in critically ill patients may be a useful intervention to avoid antibiotic-related toxicities.

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28.6 mmol/L. Sodium, potassium and chloride levels were all within normal limits.

On examination, he was afebrile, tachypnoeic (30 breaths/min) and was maintaining arterial oxygen saturations of 94% on high flow nasal prong oxygen therapy, via an Optiflow Nasal Cannula (Fisher and Paykel Healthcare, Auckland, New Zealand) with 65% oxygen. He was in atrial fibrillation but was normotensive, and he was alert and orientated. He was started on intravenous cefepime (2 g every 12 hours) and oral roxithromycin (150 mg twice daily).

Following his admission, he deteriorated and developed septic shock with progressive organ failure, and required

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ventilation for hypoxaemia. He developed acute-on-chronic renal failure (creatinine, 344  $\mu\text{mol/L}$ ; urea, 34.2  $\text{mmol/L}$ ) and was started on continuous venovenous haemofiltration (CVVH), a form of continuous RRT (CRRT). A highly permeable polyethersulfone haemofilter (Aquamax HF12 [Edwards Lifesciences, Irvine, CA]) was used, with blood flow of 200  $\text{mL/min}$ , predilution fluid 1000  $\text{mL/hr}$  and post-dilution fluid 1000  $\text{mL/hr}$ , both using Hemosol B0 (Gambro, Sondalo, Italy) solution with 18  $\text{mL}$  of 50% dextrose in each. The net fluid balance was neutral.

After receiving four doses of cefepime (8 g in total over 48 hours) the patient developed four-limb clonic seizure activity that persisted until he was treated with diazepam 10 mg intravenously. A further seizure occurred less than 1 hour later. He had no history of seizures, his blood glucose level was 10.8  $\text{mmol/L}$ , and there were no other identifiable seizure precipitants. The serum sodium level was 139  $\text{mmol/L}$ , magnesium 0.9  $\text{mmol/L}$  and phosphate 1.4  $\text{mmol/L}$ . A computed tomography scan of the brain showed only age-related atrophy, with no evidence of an acute cerebral event or mass lesion. A lumbar puncture performed 5 hours after the initial seizure showed no white cells, a glucose level of 6.3  $\text{mmol/L}$ , protein 0.28  $\text{g/L}$  and no cells on Gram stain.

The seizures were suspected to be related to cefepime toxicity, and it was discontinued. He had two further seizures later that day (a total of four) but none after that.

The patient underwent 21 days of invasive ventilation and required CRRT for a combined total of 15 days. He recovered, and left the ICU after 30 days, going to a rehabilitation ward, and was subsequently discharged to his own home after a total of 73 days in hospital. At discharge, he was free of dialysis and other organ support.

Serial blood cefepime levels and a cerebrospinal fluid (CSF) sample from the lumbar puncture were taken and later analysed (Figure 1). The cefepime concentration in the CSF taken at 300 minutes after the intravenous (IV) dose of cefepime was 6.1  $\mu\text{g/mL}$ , which corresponds to a CSF:plasma ratio at 300 minutes of about 9.1%.

The cefepime clearance was estimated at 0.82  $\text{L/hour}$ , half-life ( $t_{1/2}$ ) at 29.3 hours, volume of distribution during the terminal phase ( $V_z$ ) 34.6 L. Importantly, the CRRT was not running for two periods after the IV cefepime was given: from 120 minutes until 300 minutes, and from 1380 minutes until 1680 minutes after dosing, as seen in Figure 1.

### Discussion

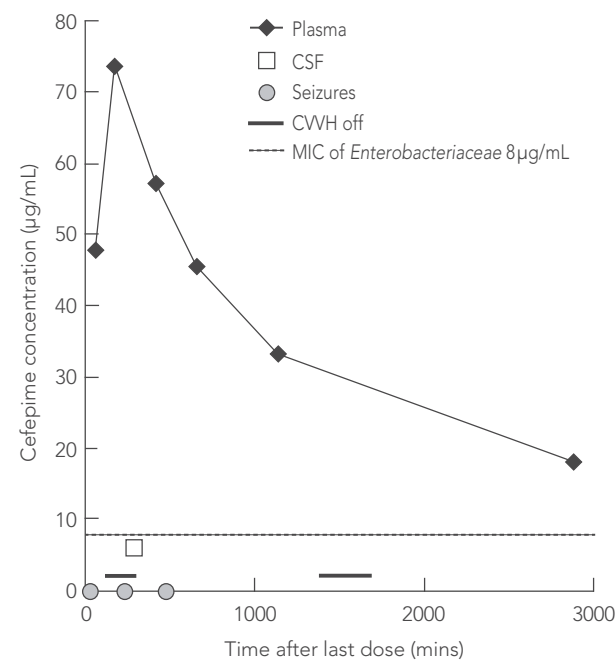
The underlying physiology involved in the transition from normal brain excitation to ictal activity is not well understood. The brain normally seems to have a "cloak" of inhibition that prevents seizures occurring. Patients in an ICU may lose this inhibition, particularly if they have toxic

concentrations of drugs that penetrate the brain and cause seizures.<sup>5</sup> This adverse event has now been reported several times for cefepime, although none of the previous articles had the frequency of sampling undertaken that this case did, nor did they have a concomitant CSF cefepime concentration measured. These data neatly show the cefepime concentrations that caused seizures, and the time-course of drug clearance and resolution of seizures, in the presence of anticonvulsive therapy.

Antibiotics can decrease central neuroinhibitory tone and subsequently lower the threshold for seizure activity. The convulsive action of cephalosporins such as cefepime is thought to be caused by the suppression of inhibitory neurotransmission via modulation of GABA(A) receptors.<sup>6</sup> As cefepime is a renally cleared antibiotic, drug clearance is significantly reduced in renal dysfunction, but enhanced in the presence of RRT.

Cefepime also seems to penetrate the blood-brain barrier well, with a CSF:serum concentration ratio of 10%.<sup>7</sup> Of course, elevated plasma, CSF and therefore cerebral cefepime levels increase the likelihood of neurological complications. During acute renal failure, cerebral concentrations increase further, due to several factors, including reduced systemic clearance, competitive inhibition of the

**Figure 1. Cefepime concentrations in plasma and cerebrospinal fluid after intravenous administration**



CSF = cerebrospinal fluid. CVVH = continuous venovenous haemofiltration. MIC = minimum inhibitory concentration.

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active transport of the antibiotic by organic acids, an increase in blood–brain barrier permeability and a decrease in serum protein binding.<sup>7</sup> Hence it is understandable that neurological complications with cefepime tend to occur with renal impairment.

As there were no other identifiable triggers, we believe that cefepime toxicity was the likely cause of our patient's seizure activity. The cefepime levels peaked at 73.8 µg/mL which, although not excessively high, may still represent a toxic level in a critically ill patient with acute renal failure. The clearance of the drug was significantly impaired, with the half-life being over 14 hours (normal is 2 hours). The delayed rise in concentration from administration is likely to have resulted from the redistribution of cefepime as a result of the CRRT being stopped for 3 hours. Seizure activity has previously been reported at plasma levels of cefepime 72 µg/mL, similar to that in our patient.<sup>8</sup> Several other reports of cefepime-associated seizure activity have also been described.<sup>7,9-12</sup>

Lipman et al<sup>13</sup> have shown that standard dosing of cefepime in septic patients with normal renal function resulted in inadequate cefepime plasma levels. This is in contrast to those patients with renal impairment who need significantly lower cefepime doses in order to prevent toxicity. This case serves to warn of the potential consequences of using high-dose therapy in the absence of robust measures of organ function and likely drug clearance. To this end, therapeutic drug monitoring (TDM) is a useful intervention. Chapuis et al<sup>8</sup> also demonstrated the difficulty of establishing correct cefepime doses for TDM in ICU patients. In their study of 30 consecutive ICU patients treated with cefepime, one-half had plasma levels considered too low to effectively treat organisms with a minimum inhibitory concentration (MIC) of 8 µg/mL. However, cefepime accumulation and neurotoxicity (non-convulsive epilepsy) also occurred in two patients with renal impairment (creatinine clearance < 50 mL/min) in spite of drug dose reduction. The risk of neurotoxicity appears to be augmented in patients with renal impairment and when dealing with less susceptible organisms requiring high concentration targets.

Another complicating factor in achieving adequate cefepime plasma concentrations in ICU patients is the addition of RRT. Haemodialysis and haemofiltration both remove cefepime from the systemic circulation, with a half-life approximating that observed in individuals with normal renal function. Estimates of the appropriate doses to obtain optimal serum concentrations can be made for the required doses during RRT, using the published pharmacokinetic data and the usual MIC of the suspected organism, as well as the dose and mode of RRT being used.<sup>14</sup> In these critically ill patients receiving RRT, not only do the doses required

differ substantially from non-critically ill patients or those without renal failure, but an individual's dosing requirements may also alter substantially over time as the patient's physiology is altered, or in the case of RRT, augmented by extracorporeal support. This dynamic process supports a utility for TDM of beta-lactam antibiotics in these patients.

TDM of beta-lactam antibiotics is being increasingly used in patients with complex pharmacokinetics.<sup>15</sup> While the principles and evidence supporting the use of TDM in ICU patients have previously been reviewed,<sup>16</sup> there are few data emphasising its capacity to identify high concentrations likely to be associated with drug toxicity. TDM was not used clinically for our patient, but his blood samples, analysed later, showed that TDM data might have informed the clinical staff of the high exposure to cefepime, and that a dose decrease could have been useful for avoiding toxicity. In the context of a patient with worsening renal function, such an approach to dose adjustment should be considered useful and has been previously suggested by Chapuis et al.<sup>8</sup>

### Conclusion

This case illustrates the challenges of drug dosing in the ICU, particularly in relation to the sequelae of toxic concentrations. Unlike other reports of cefepime neurotoxicity, the blood samples in this patient were collected very close to the last dose (minutes, not days as in other reports). These data enabled a description of the time course of decrementing concentrations from toxic to non-toxic, as well as the time frame for resolution of seizures (in the presence of anti-seizure drugs). Therefore, in the presence of difficult-to-predict pharmacokinetics (which is common for ICU patients, particularly those receiving RRT), TDM may be a useful intervention to avoid patient harm from antibiotic-related toxicities.

### Competing interests

None declared.

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References

- 1 Bilgrami I, Roberts JA, Wallis SC, et al. Meropenem dosing in critically ill patients with sepsis receiving high-volume continuous venovenous hemofiltration. *Antimicrob Agents Chemother* 2010; 54: 2974-8.
- 2 Patel K, Roberts JA, Lipman J. Population pharmacokinetics of fluconazole in critically ill patients receiving continuous venovenous hemodiafiltration: using Monte Carlo simulations to predict doses for specified pharmacodynamic targets. *Antimicrob Agents Chemother* 2011; 55: 5868-73.
- 3 Roberts JA, Field J, Visser A, et al. Using population pharmacokinetics to determine gentamicin dosing during extended daily dialfiltration in critically ill patients with acute kidney injury. *Antimicrob Agents Chemother* 2010; 54: 3635-40.
- 4 Roberts DM, Roberts JA, Roberts MS, et al. Variability of antibiotic concentrations in critically ill patients receiving continuous renal replacement therapy: a multicentre pharmacokinetic study. *Crit Care Med* 2011; 40: 1523-8.
- 5 Mirski MA, Varelas PN. Seizures and status epilepticus in the critically ill. *Crit Care Clin* 2008; 24: 115-47, ix.
- 6 Sugimoto M, Uchida I, Mashimo T, et al. Evidence for the involvement of GABA(A) receptor blockade in convulsions induced by cephalosporins. *Neuropharmacology* 2003; 45: 304-14.
- 7 Chatellier D, Jourdain M, Mangalaboyi J, et al. Cefepime-induced neurotoxicity: an underestimated complication of antibiotherapy in patients with acute renal failure. *Intensive Care Med* 2002; 28: 214-7.
- 8 Chapuis TM, Giannoni E, Majcherczyk PA, et al. Prospective monitoring of cefepime in intensive care unit adult patients. *Crit Care* 2010; 14: R51.
- 9 Martinez-Rodriguez JE, Barriga FJ, Santamaria J, et al. Nonconvulsive status epilepticus associated with cephalosporins in patients with renal failure. *Am J Med* 2001; 111: 115-9.
- 10 Wong KM, Chan WK, Chan YH, Li CS. Cefepime-related neurotoxicity in a haemodialysis patient. *Nephrol Dial Transplant* 1999; 14: 2265-6.
- 11 Dixit S, Kurle P, Buyan-Dent L, Sheth RD. Status epilepticus associated with cefepime. *Neurology* 2000; 54: 2153-5.
- 12 Sonck J, Laureys G, Verbeelen D. The neurotoxicity and safety of treatment with cefepime in patients with renal failure. *Nephrol Dial Transplant* 2008; 23: 966-70.
- 13 Lipman J, Wallis SC, Rickard C. Low plasma cefepime levels in critically ill septic patients: pharmacokinetic modeling indicates improved troughs with revised dosing. *Antimicrob Agents Chemother* 1999; 43: 2559-61.
- 14 Choi G, Gomersall CD, Tian Q, et al. Principles of antibacterial dosing in continuous renal replacement therapy. *Crit Care Med* 2009; 37: 2268-82.
- 15 Roberts JA, Hope WW, Lipman J. Therapeutic drug monitoring of beta-lactams for critically ill patients: unwarranted or essential? *Int J Antimicrob Agents* 2010; 35: 419-20.
- 16 Roberts JA, Norris R, Paterson DL, Martin JH. Therapeutic drug monitoring of antimicrobials. *Br J Clin Pharmacol* 2012; 73: 27-36. □