Case report

Ertapenem-induced encephalopathy

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SUMMARY

Neurotoxicity is an unusual side effect of carbapenems, and it has been reported most commonly presenting as seizures, encephalopathy and hallucinations. Ertapenem neurotoxicity most classically presents as seizures in patients with end-stage renal disease (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2). We present a patient with a baseline eGFR of 30–59 mL/min/1.73 m^2 with acute kidney injury who developed non-seizure neurotoxicity after ertapenem exposure. This patient is a middle-aged Caucasian man who received intravenous ertapenem for treatment of empyema. Although the empyema improved, he developed delirium beginning on day 7 of ertapenem. The delirium progressed to constant agitation and visual hallucinations requiring transfer to the intensive care unit with eventual intubation for airway protection. No improvement in mental status was observed with cessation of other medications. Ertapenem was discontinued and within 24 hours, he was extubated, and his mental status returned to baseline. He was discharged from the hospital the following day. The timely resolution after ertapenem discontinuation makes ertapenem-induced encephalopathy the most likely explanation for this patient's course.

BACKGROUND

Ertapenem belongs to the carbapenem antibiotic class, which are bactericidal agents that inhibit the formation of peptidoglycan, the amino acid and sugar polymer that make up bacterial cell walls, thus preventing proper cell wall synthesis.[1 2] Carbapenems are resistant to beta-lactamases produced by bacteria and have broad-spectrum activity against gram-negative, gram-positive and anaerobic organisms.[2] In particular, ertapenem was synthesised to specifically target anaerobic organisms and extended-spectrum beta-lactamase-producing Enterobacteriaceae. The chemical structure of ertapenem also prevents renal hydrolysis by dehydropeptidase (DHP)-1, thus increasing plasma half life and allowing for once daily dosing. It is delivered either intravenously or intramuscularly.[2 3]

Ertapenem antagonises the receptors of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in the central nervous system (CNS), and this interaction likely underlies its neurotoxic effects.[4] Most commonly, neurotoxicity from ertapenem has been associated with seizures.[5–7] Encephalopathy associated with ertapenem use is rare but has also been reported in the literature.[3 4 8–10] Encephalopathy is defined as the acute onset of diffuse cerebral dysfunction, characterised by altered mental status, loss of memory, agitation, loss of cognitive ability, insomnia and hallucinations.[11] In addition, neurotoxicity from ertapenem has frequently been described in patients with end-stage renal dysfunction (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2), as decreased renal function increases plasma ertapenem levels. Current dosing guidelines recommend a 50% dose reduction of ertapenem in patients with an eGFR <30 mL/min/1.73 m^2.[2 7 8 12 13]

We present a case of a patient with moderate chronic kidney disease (CKD) who developed non-seizure-related neurotoxicity after ertapenem treatment.

CASE PRESENTATION

A 59-year-old 65 kg Caucasian man with a history of cerebral vascular accident and myocardial infarction 3 months prior (status post stent and carotid endarterectomy with left-sided fine motor deficits in the hand), hypertension, hyperlipidaemia and stage 3 CKD (eGFR 30–59 mL/min/1.73 m^2) presented to the emergency department for evaluation of dyspnoea and right mid/upper back pain. He had a normal cognitive baseline (though no formal cognitive testing in the past) and worked as a commercial painter. He described 5–6 days of fatigue, productive cough and a new oxygen requirement at his primary physician's office that day. On evaluation in the emergency department, he was noted to have a large right-sided fluid collection with an air–fluid level on non-contrasted CT of the chest, suggestive of a complicated pleural effusion or empyema. Additionally, he was noted to have an acute injury, thought to be secondary to intravascular hypovolaemia and infection, with an admission eGFR of 22 mL/min/1.73 m^2. The diagnostic pleural fluid analysis revealed an empyema necessitating chest tube placement. The patient was treated with vancomycin (1250 mg intravenous loading dose followed by 500 mg intravenously once the following day) and ertapenem (500 mg intravenously every 24 hours), along with 3 days of intrapleural tissue plasminogen activator and dornase alfa via chest tube. Culture of the pleural fluid grew rare *Actinomyces oris*, and antibiotics were narrowed to ertapenem alone.

On hospital day 7, he began to experience nighttime delirium manifested by pulling at his chest tube, decreased orientation to place and time, and agitation. This was initially thought to be 'sundowning', and the patient was placed on hospital non-pharmacological delirium precautions with the goal of maintaining his sleep–wake cycle. However, his condition continued to deteriorate. Interestingly, on hospital day 8, the patient's ertapenem dose was increased to 1000 mg intravenously daily, as his creatinine clearance continued to improve, reaching 30 mL/min on this

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day. However, creatinine clearance worsened again the following day to 27 mL/min, and the dose was not readjusted back to 500 mg daily. Nocturnal agitation persisted and it was initially thought to be related to opioid pain medications, which were discontinued without improvement. Melatonin was started for insomnia, but his delirium worsened and he developed reversal of his sleep–wake cycle. The patient's wife confirmed no prior history of substance abuse or other mental health disorder. His empyema resolved, and his chest tube was removed during this time. By hospital day 10, ertapenem-induced encephalopathy was considered and his dose was eventually held the following day. That evening he became increasingly delirious and began having visual hallucinations (ie, was 'painting the walls' of his hospital room) and was treated with one dose each of oral and intramuscular olanzapine, without improvement. On hospital day 11, his mental status deteriorated to the point where he was unable to protect his airway requiring intubation and transfer to the intensive care unit (ICU), where he was switched to clindamycin and then to ceftriaxone. After intubation, all psychoactive medications were held aside from sedation required during mechanical ventilation (propofol and fentanyl). He required only overnight observation in the ICU and in the morning was extubated and transferred back to the medical floor with complete resolution of his delirium.

INVESTIGATIONS

Throughout these events, the patent's objective clinical data, other than his mental status, remained relatively unchanged. His vital signs (temperature, heart rate and blood pressure) all remained within normal parameters. He was never febrile nor tachycardic, therefore an infectious aetiology was thought to be less likely. Additionally, he was never hypotensive except briefly during intubation, and never required pressor support. Laboratory data included a normal arterial carbon dioxide level prior to intubation, no significant change in blood uraemia (had stable, mild elevation in blood urea nitrogen due to CKD), no significant electrolyte disturbance, normal liver function testing and no change in chronic anaemia. The patient did have a transient leucocytosis following intubation, which resolved the following day and was thought to be a demargination stress reaction rather than worsening infection or infectious encephalitis.

Workup of this patient's delirium mostly involved a more detailed history and physical examination. Initially, an acute psychiatric condition and medication-induced delirium were considered. All opiates and centrally acting medications (including the patient's chronic bupropion) were discontinued without improvement. Acute meningoencephalitis was thought to be less plausible given the patient was afebrile and had no meningeal signs. Additionally, lumbar puncture and electroencephalography (EEG) were thought to be unsafe and/or impractical prior to intubation given his extreme delirium and would have required sedation and intubation regardless. Following intubation and discontinuation of ertapenem, the patient improved so rapidly that a lumbar puncture and EEG were not thought to be necessary. Furthermore, given his rapid return to baseline and lack of focal neurological deficits, imaging of the head was not performed.

DIFFERENTIAL DIAGNOSIS

The initial differential for this patient was broad and discussed in detail earlier. It included hospital or infection-induced delirium, acute psychosis, insomnia-induced psychosis, other medication-induced psychosis, encephalitis and non-epileptiform status epilepticus.

TREATMENT

Supportive (melatonin, olanzapine and intubation/sedation).

OUTCOME AND FOLLOW-UP

The patient was discharged home on hospital day 13, only 1 day after being extubated in the ICU. He was at his functional baseline aside from generalised deconditioning from his prolonged hospitalisation, which improved with physical therapy. He had no further mental status changes or hallucinations per outpatient follow-up notes.

DISCUSSION

This is a case of ertapenem-induced encephalopathy presenting with agitation, insomnia and delirium. The rapid onset and resolution of the patient's encephalopathy were both highly temporally correlated with the initiation and discontinuation of ertapenem and without any other significant alteration in management. The Naranjo Scale, which estimates the probability of an adverse drug reaction, was used to evaluate this potential causality.[14] The Naranjo Algorithm/Scale is suggested to be less prone to subjective variations in regards to causality calculation given its relatively objective questions and numeric scoring.[15] In this case, the Naranjo Scale score (table 1) was 6, indicating this patient's encephalopathy as a probable adverse drug reaction to ertapenem. As discussed previously, alternative causes of the patient's encephalopathy were considered but thought to be less likely given the lack of objective data to suggest infection/metabolic disturbance as well as rapid onset and improvement. Despite this reasoning, alternative causes of delirium exist in this patient's case but were not evaluated given rapid improvement.

Several beta-lactam antibiotics have been described to have significant neurological side effects, including seizure and hallucinations. Interestingly, ertapenem and piperacillin present with

Table 1 Naranjo Scale of causality

Question	Yes	No	Do not know or not done	Case
Are there previous conclusive reports on this reaction?	+1	0	0	+1
Did the adverse event appear after the suspected drug was given?	+2	−1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	+1
Did the adverse reaction appear when the drug was readministered?	+2	−1	0	0 (not done)
Are there alternative causes that could have caused the reaction?	−1	+2	0	0 (investigation not done)
Did the reaction reappear when a placebo was given?	−1	+1	0	0 (not done)
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	0 (not done)
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	+1
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0 (no known history)
Total score 5–8: probable drug reaction				5

The scale is asfollows: ≥9 definite, 5–8 probable, 1–4 possible, ≤0 doubtful.

seizure activity and hallucinations as primary symptoms, whereas ceftazidime and cefepime often present with abnormal movements but without hallucinations.[16 17] In some case studies, ertapenem has also been described to cause altered mental status and agitation, as seen in this patient, along with peripheral neuropathy, acute suicidality and dystonic features.[8–10]

The chemical properties of ertapenem likely contribute to its neurotoxic effects. Ertapenem is a highly lipophilic molecule and thus easily able to penetrate the blood–brain barrier.[14] Once in the CNS, it antagonises the receptors of the inhibitory neurotransmitter GABA, specifically GABA type A receptors, resulting in diffusely decreased inhibitory transmission in the CNS.[4] The half life of ertapenem is typically 4.5 hours, after which time, 40%–50% of circulating ertapenem is cleared by the kidneys. The remainder of circulating ertapenem is largely broken down into metabolites by renal enzyme DHP-1. These metabolites continue to antagonise CNS GABA A receptors, further accentuating widespread inhibition.[4 5 12] This activity at GABA A receptors may account for ertapenem-induced encephalopathy.

Ertapenem in the setting of this patient's underlying CKD likely also contributed to the patient's development of encephalopathy. Although current ertapenem dosing guidelines recommend the reduction of dose only in patients with end-stage renal disease, those with less severe renal disease may also benefit from dose reduction. In patients with underlying CKD, excretion of ertapenem and its active metabolites is further reduced and its half life (normally 4.5 hours in patients without CKD) can be extended to between 6.1 and 14.1 hours, depending on the severity of renal dysfunction.[4 12] In addition, patients with CKD have a baseline increase in blood–brain barrier permeability, making them further susceptible to increased ertapenem activity in the CNS.[15]

This case report sheds light on the neurotoxic effects of ertapenem. Although unusual, ertapenem can lead to encephalopathy, particularly in patients with renal dysfunction. Clinicians should be aware of this potential side effect in order to identify and prevent it in high-risk patients.

Learning points

- Though carbapenem-induced neurotoxicity may be more common in patients with more advanced chronic kidney disease, it should be on the differential for any patient with an acute change in mentation.
- Early recognition of carbapenem-induced neurotoxicity can potentially reduce unnecessary investigations and diminish healthcare expenditures.
- Carbapenem-induced neurotoxicity should be further studied to gain insight into better understanding potential mechanisms that can lead to delirium.

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