Ertapenem-induced acute reversible peripheral neuropathy in chronic kidney disease: 3 case reports

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Introduction

Ertapenem is a long-acting carbapenem antibiotic with a broad spectrum activity against almost all community-acquired gram-positive and gram-negative, aerobe and anaerobe bacterial infections. Its spectrum also includes most of the hospital associated pathogens, with the exception that Pseudomonas aeruginosa, Acinetobacter spp. and Enterococcus fecalis were found much less susceptible to ertapenem than imipenem (another carbapenem) [1]. Clinical trials on complicated intra-abdominal infections, acute pelvic infections, complicated skin and soft-tissue infections, community-acquired pneumonia, and complicated urinary tract infections (UTI) demonstrated that ertapenem has equivalent efficacy and safety as ceftriaxone and piperacillin/tazobactam [2, 3]. Its high level of protein binding and serum half-life of 4 hours allow it to be dosed once daily. Ertapenem is primarily excreted by the kidneys and has a high lipophilicity and volume of distribution. Therefore, it can accumulate in patients with renal insufficiency. Thus, the recommended dose of ertapenem is reduced to 500 mg/day for patients with a glomerular filtration rate (GFR) of less than 30 mL/min/1.73 m² [4, 5]. The most common adverse effects of ertapenem are headache, diarrhoea, nausea, vomiting, rash, itching, local swelling, and inflammation at injection sites. In this article, we present 3 cases with ertapenem-induced acute reversible peripheral neuropathy despite using the recommended renal dose adjustment to emphasize a rare and life-threatening complication of this drug.
An 81-year-old man with a body weight of 65 kg was seen at our outpatient clinic with complaints of burning discomfort during urination and lower abdominal pain in 2015. He had a history of hypertensive nephropathy with stage 4 chronic kidney disease (CKD) and chronic ischemic heart disease. His current medications included metoprolol tartrate, clopidogrel, nifedipine, furosemide, and calcitriol. He was febrile (38.7°C), alert, and oriented. His initial vital signs (blood pressure (BP): 135/80 mmHg, pulse: 84/min) were normal. Urinalysis revealed 3,850 leukocytes/mm³ and 8 erythrocytes/mm³. Extended-spectrum β-lactamase (ESBL)-producing Escherichia coli was grown in urine culture. Complicated UTI was diagnosed and ertapenem 1 × 500 mg/day was administered according to the recommended dose for stage 4 CKD. Weakness, ataxia, balance disorder, and hallucinations developed after the second dose of ertapenem. Serum creatinine and estimated glomerular filtration rate (eGFR, CKD-EPI) were stable at 2.53 mg/dL and 22.9 mL/min/1.73 m², respectively. His clinical course and laboratory findings are shown in Table 1. There was no central nervous system (CNS) pathology on computed tomography (CT) scan of the brain. Electroencephalography (EEG) revealed no background alpha activity, which was pointing to metabolic encephalopathy. Electromyography (EMG) revealed axonal polyneuropathy. Since no other cause was evident, it was considered that ertapenem might be the potential culprit, and it was replaced with sefaperazon/sulbactam. Neurologic signs and symptoms resolved within 3 days of discontinuing ertapenem, and complicated UTI was cured with sefaperazon/sulbactam. EMG was repeated on day 15 and findings suggestive of neuropathy were absent.
Case 2

A 75-year-old man with type 2 diabetes mellitus, hypertension, atrial fibrillation, congestive heart failure, benign prostate hypertrophy, and stage 5 CKD on conventional hemodialysis thrice a week with arteriovenous fistula was admitted to the emergency department with complaints of new onset nausea and vomiting in 2014. His current medications included insulin, allopurinol, tamsulosin, acetylsalicylic acid, and sevelamer. He was febrile (38.6 °C), alert, and oriented. His initial vital signs (BP: 140/90 mmHg, pulse: 78/min) were stable. The rest of the physical exam was unremarkable. He received the last hemodialysis session adequately (4 hours) the day before presentation. Urinalysis revealed 3,650 leukocytes/mm³, 4 erythrocytes/mm³. His clinical course and laboratory findings are shown in Table 1. Complicated UTI was diagnosed and ceftriaxone 2 × 1,000 mg/day administered intravenously. ESBL-producing Klebsiella pneumoniae was grown in urine culture and no clinical or laboratory improvement was obtained within 3 days of antibiotic treatment; hence, ceftriaxone was replaced by ertapenem 1 × 500 mg/day according to the recommended dose for stage 5 CKD. Despite improvements in signs of infection, he developed numbness/weakness of feet and difficulty in walking (gait abnormality) following the 7th dose of ertapenem. Cranial CT scan was performed, and no CNS pathology was found. EMG revealed serious sensorimotor mixed-type polyneuropathy on axonal conduction studies of the lower extremities and the right upper extremity. Since no other identifiable cause was evident, ertapenem was discontinued. The signs and symptoms of neuropathy completely resolved within 4 days of cessation of ertapenem. Control EMG study was repeated on day 18 and showed no findings of neuropathy anymore.

Case 3

A 70-year-old man with overactive bladder and hypertensive nephropathy in stage 4 CKD presented to the outpatient clinic with a history of frequent urination, pain, and burning during urination for 2 days in 2014. His current medications included carvedilol, solifenacin, tamsulosin, and acetylsalicylic acid. He was subfebrile (37.8 °C), alert, and oriented. His initial vital signs (BP: 130/70 mmHg, pulse: 79/min) were stable. The rest of the physical exam was unremarkable. Serum creatinine and eGFR (CKD-EPI) were 2.55 mg/dL and 24.5 mL/min/1.73 m², respectively. Urinalysis revealed 26 leukocytes/mm³, leukocyte esterase 3+, 12 erythrocytes/mm³. His clinical course and laboratory findings are shown in Table 1. Enterococcus faecalis was grown in urine culture. Ertapenem 1 × 500 mg/day was initiated intravenously. Muscle weakness and difficulty in walking (gait abnormality) developed on the 7th day of ertapenem treatment. CT scan of the brain was unremarkable. Nerve conduction studies of the lower extremities revealed sensorimotor mixed-type polyneuropathy on EMG. Since no other identifiable cause was evident, ertapenem was withdrawn. Signs and symptoms of neuropathy improved within 8 days of ertapenem withdrawal. Recovery of peripheral neuropathy was confirmed by a control EMG study on the 21st day.

Discussion

In this study, we present 3 patients with stage 4 – 5 CKD who developed ertapenem associated acute reversible peripheral neuropathy that was proven with electroencephalography and electromyography. All patients received dose adjustment as recommended for CKD, and signs and symptoms of peripheral neuropathy disappeared without any sequels within 2 weeks of withdrawal of ertapenem.
lated to its action on the α-amino-3-hydroxy-5-methyl-isoxazolepropionate (AMPA) and N-methyl-D-aspartate (NMDA) receptor complexes and the basicity of the amino functional group of the C-2 side chain. Differences between carbapenems in the C-2 side chains may result in varying binding affinities for GABA receptors in the CNS. Compared with other carbapenems, ertapenem has a higher protein binding capacity and a larger volume of distribution due to a meta-substituted benzoic acid group at position-2, which increases its molecular weight and lipophilicity [7]. Clearance of ertapenem is mostly (80%) by the kidneys and total clearance of ertapenem decreases in a linear fashion with declining GFR. The half-life of ertapenem can be extended from 4.5 hours in patients with normal renal function to 6.1 – 14.1 hours in patients with CKD. Moreover, increased permeability of the blood-brain barrier in patients with uremia can facilitate the penetration of ertapenem into the CNS [5]. Therefore, the recommended daily dose of ertapenem is reduced to 500 mg (from 1,000 mg) for patients with stage 4 or 5 CKD or GFR of < 30 mL/min/1.73 m² [4, 5]. According to the manufacturers, seizures occurred in 0.5, 0.7, and 0.5% of patients who were exposed to ertapenem, meropenem, and imipenem/cilastatin, respectively [8]. Data from 7 clinical trials on ertapenem revealed an average seizure incidence of 0.18% [9, 10]. Our 3 cases had stage 4 or 5 CKD and developed acute neurological symptoms after using ertapenem with renal dose adjustment. Signs and symptoms of case 1 (ataxia, balance disorder and hallucinations) were pointing to CNS involvement, whereas symptoms of peripheral neuropathy (numbness-weakness of feet and difficulty in walking) developed in case 2 and case 3. CT scans of the CNS were unremarkable in all patients. EEG revealed no background alpha activity in case 1, which was consistent with metabolic encephalopathy. Uremic encephalopathy was not considered because the renal functions in all patients were stable throughout the clinical courses. There was not any identifiable cause other than administration of ertapenem. Furthermore, dramatic improvement in signs and symptoms of neuropathy upon discontinuation of ertapenem and recovery of axonal neuropathy on follow up EMG studies were in support of ertapenem induced acute reversible neuropathy. Clinical course and laboratory findings of all patients are shown in Table 1.

Although ertapenem associated neurotoxicity is well known to occur with excessive doses, very few cases of neurotoxicity were reported when it is used according to the recommended dose adjustment. Seto et al. [11] reported a 56-year-old white man with end-stage renal disease requiring continuous ambulatory peritoneal dialysis who experienced 5 episodes of seizures following 2 doses of 500 mg ertapenem intravenously. They concluded that clinicians administering ertapenem to patients undergoing peritoneal dialysis should use caution. Shea et al. [12] reported a patient with moderate renal impairment who developed ertapenem-induced encephalopathy and delayed recovery up to 2 weeks, despite using renal dose adjustment. The patient was managed conservatively with complete clinical recovery. They concluded that ertapenem can induce prolonged encephalopathy in patients with moderate renal impairment and these patients can be managed conservatively with the expectation of complete recovery. Wen et al. [13] reported two cases of acute prolonged neurotoxicity associated with ertapenem in patients with stage 5 CKD not yet on dialysis. The 2 patients developed progressive hallucinations, asterixis, myoclonic jerks, and cognitive impairment within 4 days of receiving reduced dose of 500 mg/day ertapenem according to the recommended dose adjustment for CKD. Authors found that the plasma ertapenem level was 53.7 mg/L 24 hours after the last dose in one of their patient, which was much higher than the therapeutic MIC90 (2 mg/L). Neurologic manifestations lasted for 2 weeks, despite cessation of ertapenem and initiation of high-flux hemodialysis. Authors highlighted that the structural and pharmacokinetic characteristics of ertapenem such as its high lipophilicity, central nervous penetration, and volume of distribution contributed to sustained neurotoxicity despite significant reduction in plasma ertapenem levels with high-flux hemodialysis. They concluded that although 500 mg/d ertapenem has been recommended for patients with a glomerular filtration rate of less than 30 mL/min/1.73 m², this dose may still be excessive for patients with stage 5 CKD, especially those who are not yet on dialysis.
Since all cases in our study were male and > 65 years old, we think that advanced age and male gender could be potential risk factors for ertapenem induced neurotoxicity even when it is used with the recommended dose reduction. We believe that our patients were unique for several reasons. To the best of our knowledge, the occurrence of acute, rapidly reversible peripheral neuropathy associated with ertapenem treatment has not been well characterized before. Although 1 patient (case 1) had additional signs and symptoms of CNS involvement (ataxia, balance disorder, and hallucinations), none of the patients developed seizure. All patients had acute reversible peripheral neuropathy (case 1 axonal motor neuropathy, case 2 and 3 sensorimotor mixed type polyneuropathy). Moreover, the duration of recovery following withdrawal of ertapenem in our patients was shorter (3, 4 and 8 days for case 1, 2 and 3, respectively) than in other reports which lasted for 2 weeks. None of our patients had any sequel after discontinuing ertapenem. Better renal functions in our patients as compared with the other reports [11, 13] might be a reason for these disparities. We could not measure plasma ertapenem levels and this was a limitation of this study.

**Conclusion**

As with other carbapenems, ertapenem is potentially neurotoxic in patients with renal failure, even when its dose is adjusted according to the recommendations. Although carbapenem-related neurotoxicity most commonly manifests as seizures, our study demonstrated that acute, reversible peripheral neuropathy can also develop. Clinicians administering ertapenem to patients with stage 4 or 5 CKD should be cautious of this adverse effect.

**Conflict of interest**

The authors declare that they have no competing interests.

**References**


