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Case Report

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Convulsion due to Ertapenem in a Renal Transplant Patient

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Abstract

A new generation carbapenem, ertapenem has an important advantage as it can be administered once a day. Among carbapenems imipenem is known to have neurotoxic side effects and reduces the seizure threshold in the kidney diseases' patient population. Rare cases of ertapenem neurotoxicity have been reported. We present a 53-year-old kidney transplant recipient with generalized convulsions who had renal dysfunction and was under ertapenem treatment due to urinary tract infection.

Keywords: Convulsion, ertapenem, renal transplantation

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INTRODUCTION

Kidney transplantation is the most exclusive treatment for end-stage renal disease. Since the immune system of patients undergoing kidney transplant is suppressed, opportunistic and treatment-resistant infections commonly occur. The carbapenem group of antibiotics are highly preferred for such patients. Among these agents, ertapenem is a relatively new carbapenem, which was licensed in Europe in 2002 and has a narrower spectrum compared to other carbapenems (1). Due to its resistance to hydrolysis with penicillinase, cephalosporinase, and broadspectrum beta-lactamases, it is considered a broad-spectrum antibiotic effective against gram-positive and -negative microorganisms (2). It can be used for complicated skin infections, community-acquired pneumonia, complicated urinary tract infections, and intra-abdominal and pelvic infections. The greatest advantage of ertapenem over other carbapenems is that it can be administered as a single dose daily due to its long half-life. Therefore, it is the frequently preferred antibiotic.

The carbapenem group antibiotics, including ertapenem, are agents that may rarely have neurotoxic effects, but the neurotoxic side effects of carbapenems are known to be higher than other B-lactam group of antibiotics (3). Convulsive seizures are the most common neurotoxic side effects, and visual–auditory hallucinations, agitation, and changes in the state of consciousness are some of the non-convulsive neurotoxic side effects (3). Imipenem–cilastatin commonly cause convulsions among the carbapenems with a rate of 3%-33%. Ertapenem rarely causes convulsions with a rate of 0.5% (4); however, in some cases, such as renal dysfunction, advanced age, and polypharmacy, the risk of ertapenem-associated seizures increases (5).

Here, we present a rare case of convulsion and neurotoxicity associated with the use of ertapenem in a kidney transplant patient.

CASE PRESENTATION

A 53-year-old male patient who had kidney transplantation from a live donor 3 years ago was admitted to our hospital with the complaint of diarrhea for 3 days. The serum creatinine levels were found to be 2.5 mg/dL in the last year. Laboratory findings at the admission were as follows: blood urea nitrogen (BUN): 27 mg/dL, creatinine: 5.5 mg/dL, sodium (Na+): 140 mEq L, potassium (K+): 4 mEq/L, white blood cell count: 8400/mm^3, hemoglobin (Hgb): 9.9 mg/dL, platelet count: 180,000/mm^3, C-reactive protein: 11.3 mg/dL (normal range, 0-5). The patient had been receiving tacrolimus 1.5 mg/day, mycophenolate mofetil 2 g/day, and prednisolone 5 mg/day. He was hospitalized and intravenous (IV) hydration with 2000 cc/day 0.9% sodium chloride was started due to gastroenteritis-induced dehydration. His regular medications were continued at the same dose. The serum creatinine level increased to 8.13 mg/dL during the follow-ups. Hydration was continued. In the follow-up, urinary tract infection was observed and 100.000 colonies of extended spectrum beta-lactamases (ESBLs) (+) *Escherichia coli* were detected in a urine culture, and the patient was started on IV ertapenem 500 mg/day at a renal dose on the seventh day of his admission. The patient, without any known epileptic diseases, developed generalized convulsive seizures after 3 days of ertapenem treatment. Convulsion was intervened by IV diazepam 5 mg, and the laboratory findings of the patient of that day were serum BUN: 42 mg/dL, creatinine: 7.4 mg/dL, Na: 137 mEq/L, K: 3.7 mg/dL, aspartate aminotransferase: 16 U/L, and alanine aminotransferase (ALT): 11 U/L. He had no metabolic acidosis. Brain tomography and diffusion magnetic resonance, which were evaluated by the Neurology Department, were normal. Since the patient did not have any metabolic or organic pathology for the convulsion and the condition was thought to be related to the use of ertapenem, the treatment was discontinued and switched to IV meropenem 500 mg/day for urinary tract infection. The Naranjo adverse drug reaction probability scale score used to evaluate the relationship between the patient's convulsive seizures with ertapenem was 6, and hence it was interpreted as a probable drug reaction (Table 1). Following the recurrence of the convulsion on the next day, the patient was started on valproic acid with a loading dose of 2 g IV followed by an IV infusion of 2 g for 24 hours with the recommendation from the Neurology Department. The patient had two more convulsions on the same day. He had generalized convulsive seizures 5 times for 3 days, and no seizures developed after the third day. Oral 2×500 mg valproic acid treatment was continued. In the follow-up, due to the absence of improvement in the renal function and low urine output, hemodialysis was performed. The patient developed hospital-acquired pneumonia during the follow-up period and died after 1 month. Informed consent was obtained from the patient who participated in this study.

DISCUSSION

We present a case of convulsive seizure probably due to the use of ertapenem in a patient who had undergone kidney transplantation and had worsened renal function due to urinary tract infection.

Renal transplant patients are susceptible to infections due to the use of immunosuppressive drugs, and skin infections,

Table 1. Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Do Not Know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	+1
Did the adverse event appear after the suspected drug was administered?	+2	−1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
Did the adverse event reappear when the drug was readministered?	+2	−1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0	+2
Did the reaction reappear when a placebo was given?	−1	+1	0	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	0
[a]Total score:				6

Naranjo Adverse Drug Reaction Probability Scale is interpreted as total score <0: doubtful drug reaction; 1-4: possible drug reaction; [a]5-8: probable drug reaction; 9-13: definite drug reaction (10)

community-acquired pneumonia, and complicated urinary tract infections are common in this group of patients. Patients develop multiple antibiotic-resistant infections because of frequent infections, long hospital stay, and long-term antibiotic use. Carbapenems are frequently used in the treatment against the multi-antibiotic-resistant microorganisms. Among the carbapenems, ertapenem is commonly preferred by physicians as it is a narrow effect spectrum and can be administered once a day.

Carbapenems may be neurotoxic. It is thought that the neurotoxicity of carbapenems is related to the degree of binding of the C-2 amino groups to the gamma aminobutyric acid A receptor, and therefore imipenem with the simpler C-2 amino group causes a higher rate of neurotoxicity. Similarly, ertapenem is expected to be the carbapenem with the lowest neurotoxic effect due to the acidic carboxyl group in the C-2 side chain (6-8). The most common neurotoxic side effects are convulsive seizures. Imipenem often causes convulsions, whereas ertapenem rarely causes convulsions (4).

Several risk factors for carbapenem neurotoxicity have been described previously. The most important risk factor associated with the patient is the presence of renal dysfunction. Other risk factors include a history of central nervous system disease, advanced age, and low body mass index (6). In healthy individuals, approximately, 80% of ertapenem is excreted via the kidney (3). In cases where the glomerular filtration rate is less than 30 mL/min, it is recommended to reduce the dose of ertapenem by 50%, but despite dose reduction, the presence of renal dysfunction is the most important risk factor for ertapenem neurotoxicity.

Drug interactions in the neurotoxicity of ertapenem have also been reported. Ertapenem shows renal tubular secretion similar to other B-lactam group antibiotics. Therefore, it is possible that drugs, such as probeniside, salicylate, and indomethacin that competitively inhibit renal tubular secretion can increase the level of serum ertapenem, thereby increasing ertapenem neurotoxicity (4, 9). Another drug-related condition is the extensive binding of ertapenem to plasma proteins. Therefore, it is speculated that the use of other drugs that bind strongly to plasma proteins may increase free ertapenem level in the serum, thereby increasing neurotoxicity, but there is no clear evidence.

In patients with renal transplantation, renal dysfunction due to chronic rejection in the long term is common. This condition increases the risk of ertapenem neurotoxicity similar to the present case. Moreover, in the case of low body weight with chronic kidney disease, the drug dose may be high and may result in increased neurotoxicity. In addition, it is known that ertapenem decreases serum tacrolimus level, but the effect of the immunosuppressive drugs used after renal transplantation on the level of ertapenem is not exactly known. In a recent study by Lee et al., in the patient population with normal renal function, a stroke history, anemia, and thrombocytopenia were considered risk factors for ertapenem-induced convulsions, whereas the use of steroids was considered protective (5). Our patient also had anemia as an additional risk factor.

The pharmacological agents other than medications regularly used for kidney transplantation and IV 500 mg/day ertapenem to treat the ESBL (+) *E. coli*-mediated urinary tract infection are not given from the time of hospitalization of the patients until the onset of convulsions. The convulsions, which developed 3 days after the start of ertapenem treatment and lasted for 3 days, were thought to be clinically related to ertapenem. The Naranjo adverse drug reaction probability scale for assessing the likelihood of drug side effects was used to evaluate the relation of the seizures with ertapenem (10). The seizures were found to be probably due to the drug reaction as the Naranjo scale score was 6. Neurotoxicity due to ertapenem is very rare in the renal patient population and is presented as case reports (11, 12). Our case is the first to describe the side effect of neurotoxicity in a kidney transplant patient.

CONCLUSION

As a result, renal function and haemoglobin and platelet levels should be considered if ertapenem is preferred with necessary indications or empirically in a kidney transplant population with an increased risk of infection.

Informed Consent: Informed consent was obtained from the patient who participated in this study.

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