



## Imipenem-associated seizure in a patient operated for left-sided colon tumor

### Sol kolon tümörü nedeniyle opere edilen hastada imipenem ilişkili nöbet

Mehmet Tolga Kafadar<sup>1</sup>, Abdullayev Mirsaleh Miryaguboglu<sup>2</sup>, Serdar Gencler<sup>3</sup>, Hatice Kilinc<sup>4</sup>, Meral Sen<sup>1</sup>

<sup>1</sup>Turgut Özal University, Faculty of Medicine, Department of General Surgery, Ankara, Turkey

<sup>2</sup>Azerbaijan Medicine University, 3rd Department of General Surgery, Baku, Azerbaijan

<sup>3</sup>Turgut Özal University, Faculty of Medicine, Department of Neurology, Ankara, Turkey

<sup>4</sup>Turgut Özal University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Ankara, Turkey

#### Abstract

Although the pathophysiology of drug-associated seizures involves many factors, it mainly depends on the culprit drug and case-specific factors. There is usually no previous history of epilepsy in these patients, and epileptic seizures are due to lowering in epileptic threshold by the culprit drug. Epileptic seizures usually do not recur when the culprit agent is discontinued. Convulsion is a rare side effect of beta-lactam antibiotics. The neurotoxic side effects of carbapenem group antibiotics are thought to occur through an interaction with amino butyric acid receptors. Meropenem and imipenem are also a carbapenem group antibiotic. A 61-year-old man who developed a postoperative wound infection after being operated for left colon tumor had *Klebsiella Pneumoniae* proliferation in culture antibiogram and was put on imipenem/cilastatin treatment. He developed seizures with tonic-clonic convulsions on the fourth day of treatment, and the seizures were attributed to the imipenem/cilastatin treatment. No other pathology suggestive of seizure etiology could be found in his examinations. His antibiotic regimen was changed to a different one and he was discharged in good health on the 11<sup>th</sup> day of his hospital admission.

**Keywords:** Antibiotherapy; Imipenem; Seizure.

#### Öz

İlaç ilişkili nöbetlerin patofizyolojisi birçok faktörü içermekle birlikte esas olarak kullanılan ilaç ve olgu faktörüne bağlıdır. Bu tip olgularda bilinen epilepsi öyküsü yoktur, kullanılan ilacın epileptik eşiği düşürmesine bağlı olarak epileptik nöbetler görülür. Sorumlu ajanın kesilmesiyle genelde nöbet tekrarlanmaz. Beta-laktam antibiyotiklerin nadir görülen yan etkilerinden biri de konvülsiyondur. Karbapenem grubu antibiyotiklerin nörotoksik yan etkilerinin, gamma amino bütirik asit reseptörleri ile etkileşim sonucu geliştiği sanılmaktadır. Meropenem ve imipenem de karbapenem grubu antibiyotiklerdir. Kliniğimizde sol kolon tümörü nedeniyle opere edilen ve postoperatif yara yeri enfeksiyonu gelişen 61 yaşındaki erkek hastada, kültür antibiogramda *Klebsiella Pnömonia* üredi. Tedavide imipenem/silastatin başlandı. Tedavinin 4. günü tonik-klonik kasılmalarla seyreden nöbet gelişti. Nöbet, imipenem/silastatin tedavisine bağlandı. Antiepileptik tedavi verilen hastada, yapılan tetkiklerde konvülsiyonu açıklayacak başka bir patoloji bulunamadı. Antibiyotik tedavisi değiştirilen hasta, yatışının 11. günü şifa ile taburcu edildi.

**Anahtar Kelimeler:** Antibiyoterapi; İmipenem; Nöbet.

Received/Başvuru: 12.03.2016  
Accepted/Kabul: 07.04.2016

#### Correspondence/İletişim

<sup>1</sup>Turgut Özal University, Faculty of Medicine, Department of General Surgery, Ankara, Turkey  
E-mail: drtolgakafadar@hotmail.com

#### For citing/Atıf için

Kafadar MT, Miryaguboglu AM, Gencler S, Kilinc H, Sen M. Imipenem-associated seizure in a patient operated for left-sided colon tumor. J Turgut Ozal Med Cent 2016;23(3):339-41.

## INTRODUCTION

Beta-lactam antibiotics are widely preferred for the treatment of infectious diseases as a result of their extended spectrum and high antibacterial efficacy. Imipenem is a beta-lactam antibiotic and a member of carbapenem group (1). As it is broken down by the dihydropeptidase enzyme in kidneys, it is administered with cilastatin, a dihydropeptidase inhibitor, in clinical use (2). The most common side effects of imipenem/silastatin (I/S) are nausea, vomiting, allergic reactions, diarrhea, injection site phlebitis, liver enzyme elevation, and eosinophilia. Additionally, it may cause convulsions in alcoholics, persons with central nervous system (CNS) diseases, and persons using this drug in high doses (3). In this paper, we report a 61-year-old patient free of any central nervous system disease who had convulsions due to high-dose imipenem use for wound site infection caused by *Klebsiella pneumonia* after being operated for left-sided colon tumor.

## CASE REPORT

A 61-year-old male presented at the emergency department with abdominal pain and constipation. Abdominal physical examination revealed diffuse tenderness and guarding. Abdomen was also distended. Abdominal tomography and colonoscopy performed for a preliminary diagnosis of ileus revealed a mass lesion obstructing the lumen of the left colon; the patient was operated with hemicolectomy + end-to-end colocolic anastomosis under emergency conditions. Pathology result was consistent with adenocarcinoma of the left colon. As hyperemia and discharge were detected at midline incision 6 days after the operation, the sutures around the umbilicus were re-opened. Laboratory tests were normal except for WBC and CRP elevation. He had no fever. Wound site culture was taken. ESBL positive *Klebsiella pneumonia* was proliferated in the culture. The strain was sensitive to imipenem, ertapenem, and ciprofloxacin but resistant to ceftriaxone and ampicillin. The department of infectious diseases was consulted and imipenem 4x500 mg was begun. The control whole abdomen tomography did not detect any collection or focus of abscess. While being followed with daily wound dressings, the patient developed sudden-onset generalized tonic-clonic convulsions at the fourth day of therapy. He was consulted with the neurology department and a cranial tomography and an EEG (electroencephalogram) were obtained. Cranial tomography did not reveal bleeding or acute cerebral pathology. EEG did not show any pathology suggestive of the origin of convulsions. The patient was put on Sodium Valproate 500 mg bid. Imipenem treatment was immediately stopped and Meropenem 1g tid was begun in line with the recommendation of the department of infectious diseases. Having an improved overall status, normalized WBC and CRP levels, and no recurrence of convulsions, the patient was discharged on the 11<sup>th</sup> day of admission, with a control visit scheduled for some time later.

## DISCUSSION

Convulsions are involuntary epileptic seizures produced by abnormal neuronal discharge. I/S-induced convulsion has a reported incidence of 1.5% to 3% (4). Despite the obscurity of the mechanism behind I/S treatment leading to convulsion, it is thought to be multifactorial of origin. The convulsive effects of beta-lactam antibiotics have been shown in studies both on rats and humans (5, 6, 7).

Imipenem was reported to reduce the inhibition of epileptic discharge by binding to the receptors of gamma aminobutyric acid, the major inhibitor transmitter in CNS (4,8). Prior studies have shown that the convulsive effect of carbapenem derivatives is produced by its 1-methyl subgroup which is a part of the C-2 side chain in their structure (9). The convulsive effect of imipenem has been reported to be more exaggerated than that of other beta-lactam antibiotics (10). Convulsion risk is usually associated with high-dose use of the drug. Moreover, central nervous system injury, renal functional disorders, senility, electrolyte disorders, and simultaneous use with nephrotoxic antibiotics such as vancomycin, amikacin facilitates the genesis of convulsions (2, 11).

Horiuchi et al. (5) reported that intravenous I/S at a total dose of 200/200 mg/kg produced no epileptic behavior in rats while tonic-clonic convulsions were produced by a dose of 400/400 mg/kg. Koppel et al. (4) in a 75-patient study, observed seizure activity in 4 patients during imipenem treatment at a dose of 2 g/day. Our patient suffered tonic-clonic convulsions after the administration of I/S at a dose of 4x500 mg/day from the beginning of the treatment to fourth day. The patient was resuscitated without being intubated and connected to mechanical ventilator. In the present case, convulsion development was linked to high-dose I/S treatment.

Patients taking I/S treatment should be carefully monitored for total drug dose administered. If convulsions occur during treatment, it should be immediately stopped. Other possible organic reasons for convulsion development should be sought. In cases when no organic cause can be determined, imipenem-induced convulsion should be considered.

## CONCLUSION

Before commencing imipenem treatment for any indication in patients operated at general surgery clinics, it should be remembered that imipenem-induced convulsion may occur. The offending antibiotic should be immediately switched to another if convulsions arise, and other possible etiologies for convulsion should be investigated.

## REFERENCES

1. Chambers HF. Carbapenems, 'Mandell GL, Bennett JE, Dolin R (eds). Principles and Practice of Infectious Diseases, 6th edition'. Elsevier's Health Sciences, Philadelphia 2005:311-4.

2. Akisü M, Kültürsay N, Çoker C, Akisü Ç, Baka M. Amino acid neurotransmitter levels in the cerebral cortex of mice receiving imipenem/cilastatin. Lack of excitotoxicity in the central nervous system. *Tr J Med Sci* 1998;28(5):495-8.
3. Calandra GB, Brown KR, Grad LC, Ahonkhai VI, Wang C, Aziz MA. Et al. Review of adverse experiences and tolerability in the first 2516 patients treated with imipenem/cilastatin. *Am J Med* 1985;78(6A):73-8.
4. Koppel BS, Hauser WA, Politis C, van Duin D, Daras M. Seizures in the critically ill: the role of imipenem. *Epilepsia* 2001;42(12):1590-3.
5. Horiuchi M, Kimura M, Tokumura M, Hasebe N, Arai T, Abe K. et al. Absence of convulsive liability of doripenem, a new carbapenem antibiotic, in comparison with betalactam antibiotics. *Toxicology* 2006;222(1-2):114-24.
6. Akpınar CK, Dogru H, Cengiz N. Epileptic seizure associated with drugs: Report of two cases. *Gaziantep Med J* 2015;21(3):219-20.
7. Oktan B, Kısabay A, Yılmaz H. Triggered Epileptic Seizured with Imipenem: Case Report. *Turkiye Klinikleri J Neur* 2013;8(1):24-30.
8. Bustamante CI, Drusano GL, Tatem BA, Standiford HC. Postantibiotic effect of imipenem on *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 1984;26(5):678-82.
9. Hikida M, Masukawa Y, Nishiki K, Inomata N. Low neurotoxicity of LJC 10627, a novel 1b-methyl carbapenem antibiotic: Inhibition of g-aminobutyric acid A2, benzodiazepine, and glycine receptor binding in relation to lack of central nervous system toxicity in rats. *Antimicrob Agents Chemother* 1993;37(2):199-202.
10. Miller AD, Ball AM, Bookstaver PB, Dornblaser EK, Bennett CL. Epileptogenic potential of carbapenem agents: mechanism of action, seizure rates and clinical considerations. *Pharmacotherapy* 2011;31(4):408-23.
11. Karadeniz C, Oguz A, Canter B, Serdaroglu A. Incidence of seizures in pediatric cancer patients treated with imipenem/cilastatin. *Pediatr Hematol Oncol* 2000;17(7):585-90.