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Corresponding author:

Hwan Jun Choi
Department of Plastic and
Reconstructive Surgery, Soonchunhyang
University Hospital Cheonan, 31
Sooncheonhyang 6-gil, Dongnam-gu,
Cheonan 31151, Korea
Tel: +82-41-570-2195
Fax: +82-41-574-6133
E-mail: 71830@schmc.ac.kr
ORCID:
<https://orcid.org/0000-0002-0752-0389>

Cefepime-induced neurotoxicity after flap surgery: a rare case report

Woo Jin Song¹, Chan Yeong Lee¹, Hyeong Rae Ryu², Je Yeon Byeon²,
Hwan Jun Choi^{2,3}

¹Department of Plastic and Reconstructive Surgery, Soonchunhyang University Seoul Hospital, Korea

²Department of Plastic and Reconstructive Surgery, Soonchunhyang University Cheonan Hospital, Cheonan, Korea

³Institute of Tissue Regeneration, Soonchunhyang University College of Medicine, Cheonan, Korea

Cefepime is a fourth-generation cephalosporin that covers gram-positive bacteria and gram-negative bacteria, such as *Pseudomonas*. A 48-year-old male patient underwent a posterior tibial artery perforator-based fasciocutaneous turnover flap and was administered cefepime. After 2 days, the patient showed neurological symptoms, such as cognitive decline and aphasia. We immediately stopped cefepime and changed to ciprofloxacin. In addition, thiamine was administered and additional dialysis was performed. The neurological symptoms were resolved after tapering cefepime and hemodialysis. In patients undergoing flap surgery, especially those with impaired renal function, cefepime should be administered carefully considering the risk of neurotoxicity.

Keywords: Cefepime, Drug-related side effects and adverse reactions, Neurotoxicity syndromes

Introduction

The use of antibiotics for prophylactic or therapeutic purposes is common in surgery. As prophylactic antibiotics, cephalosporine or ampicillin-sulbactam are mainly used [1]. If a specific bacterium is suspected, proper antibiotics should be selected. Cefepime is a broad-spectrum 4th generation cephalosporin with an enhanced effect on gram-positive and -negative bacteria. It is particularly good for bacteria producing extended-spectrum β -lactamase such as *Pseudomonas* [2]. It has relatively common adverse effects such as headache, nausea, and rash, and cefepime-induced neurotoxicity (CIN) is the most important adverse effect to watch out for. Cefepime passes through the blood-brain barrier and can exhibit neurotoxicity, showing various clinical features such as cognitive decline, encephalopathy, aphasia, and convulsions. CIN occurs particularly more commonly in patients with decreased renal function [3]. It should be noted that it is difficult to differentiate from an acute stroke in elderly patients. This neurotoxicity usually resolves within a few days after cefepime is discontinued, but in special cases, it is an important factor that can also affect the course of surgery [4]. In our case, cognitive decline, aphasia, delirium, and seizure occurred in a patient who received cefepime in a renal-adjusted dose after flap surgery and was finally diagnosed as CIN through an electroencephalogram (EEG). Seizure occurred after flap surgery, where movement is completely restricted, and congestion of the flap site occurred due to movements and pressure. It made the flap site take a long time to be healed. Herein, the authors have experienced a case of CIN that affected the

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course of the flap surgery and report it as an educational case.

Case report

This study is a retrospective case review. The study protocol was approved by the Institutional Review Board of Soonchunhyang University College of Medicine (No. 2021-03-026). Written informed consent for publication of the clinical images was obtained from the patient. All medical records in the study involving human participants were reviewed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

A 48-year-old male patient visited the outpatient clinic due to a painful skin defect on the left lateral malleolar area that occurred spontaneously 4 months ago. The defect was oval-shaped and about 6×5 cm in size (Fig. 1). The patient had a



Fig. 1. Photograph of the initial finding. Gross preoperative photographic image with the raw surface of the lateral malleolar area.

medical history of diabetes mellitus and chronic kidney disease receiving dialysis three times a week. However, the patient had no trauma history around his left lateral malleolar area. On physical examination, wet debris and greenish discharge suspecting pseudomonal infection were suspected on the defect. Because bacteria were not identified through culture test, initially a broad-spectrum antibiotic therapy that combines vancomycin and piperacillin/tazobactam was administered. Daily wound irrigation was performed, and the wound gradually cleared up. So, the patient underwent a posterior tibial artery perforator-based fasciocutaneous turnover flap. A greenish discharge was still observed after surgery, and *Pseudomonas* bacteria were cultured from the discharge. As a result of the resistance of the cultured bacteria, cefepime was the most sensitive to the isolated strain. Accordingly, we de-escalate the antibiotics to cefepime 1 g per 12 hours with consultation to Department of Infectious Diseases. On postoperative day 1, the flap has intact Doppler sound and was kept pinkish and warm, presuming to have a good blood flow. Also, the capillary refilling time was about 1 to 2 seconds (Fig. 2A). On the evening of the day starting cefepime, the patient suddenly showed aphasia and depressive mood. Unlike before, the patient was unable to communicate normally. The D-dimer test was performed but it was normal, and no specific findings were observed in other laboratory findings. Chest computed tomography (CT) and brain CT were performed and there were no abnormal findings. On postoperative day 2, the patient had a seizure and delirium. Originally, the patient was absolutely on bed rest to maintain the flap, but the operation site was pressed due to severe movements due to seizure. We tried to control it with restraints and antidelirium agents, but it was clinically difficult to avoid compression using restraints for the lateral malleolar area, and there was little response to medical treatment. So, flap area generally



Fig. 2. Photograph of postoperative findings. (A) The flap is healthy with pale-pinkish skin color and normal turgor on postoperative day 1. (B) On postoperative day 2, there is diffuse congestion on the flap site. (C) On postoperative day 31, the congestion was resolved and the grafted skin was taken-up.

turned purple, and congestion progressed (Fig. 2B). EEG was performed to find the cause, and triphasic waves and slowing were observed. This suggested metabolic encephalopathy, and we suspected cefepime as the cause. We immediately stopped cefepime and changed to ciprofloxacin 400 mg per day. In addition, thiamine 2 g per 12 hours was administered and additional dialysis was performed. After 2 days, the patient's symptoms all improved. The Doppler sound through the skin paddle did not change, and because it is a pedicled flap, the pedicle patency was judged to be intact. So instead of surgical exploration, congestion of the flap site was treated with lesional heparin injection and dressing with heparin gauze, and a heating lamp was also applied. The congestion of the central portion except for distal margins was gradually resolved. On postoperative day 10, the superficial necrotic tissue was removed, and the rest of the defective surface underwent a skin graft. The lesion was finally healed, and the patient was discharged 21 days after the surgery (Fig. 2C). On the 6-month follow-up, the patient had no neurologic symptom or other complications.

Discussion

Cefepime is a broad-spectrum fourth-generation cephalosporin, showing an enhanced effect on gram-positive bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae*, and a good effect on gram-negative bacteria producing extended-spectrum β -lactamase such as *Pseudomonas* [2]. Possible adverse events include headache, nausea, rash, and diarrhea. The most important side effect is neurotoxicity, and the incidence rate is increasing recently. The main risk factors for CIN include decreased renal function, drug overdose, severe illness, alteration in the blood-brain barrier, organic brain damage, and old age [3]. Most of the cases occur due to poor dose control in patients with decreased renal function, but caution should be made because it can occur even when the renal function is normal or when the dose is adjusted according to the renal function [4]. The incubation period of neurotoxicity due to cefepime varies from 1 to 30 days after drug initiation. As a symptom of neurotoxicity, cognitive decline is the most common and can appear in various aspects such as encephalopathy, aphasia, delirium, seizure, and coma [3]. A clinical convulsion may show generalized tonic-clonic seizure, complex partial seizure, or focal seizure in patterns, and it may be expressed as non-convulsive status epilepticus or myoclonus [5]. The patient in this case also showed neurological symptoms such as cognitive decline, aphasia, depression, and convulsions 2 days after administration of cefepime.

When CIN is suspected, a blood drug concentration test and EEG can be performed. When the drug concentration in the blood increases due to a decrease in glomerular filtration rate or an excessive dose compared to the renal function, it becomes a risk factor for the occurrence of neurotoxicity. According to previous reports, neurotoxic side effects did not occur when cefepime trough concentration was less than 7.7 mg/L, and neurotoxicity always occurred when it was above 38.1 mg/L [6]. In this case, since all patient's symptoms improved rapidly, no additional drug concentration test was performed. Although the patient had a decline in renal function, CIN occurred even with the appropriately renal-adjusted dose, so this possibility should always be considered. In the patient with CIN, EEG can appear in various ways. According to previous reports, generalized periodic discharge with or without triphasic morphology was the most common EEG pattern, followed by generalized rhythmic delta activity and generalized spike-and-waves [5]. In this case, EEG findings with triphasic morphology and slowing were observed.

If an elderly patient exhibits these neurotoxic symptoms, it may be difficult to distinguish them from other causes. In particular, the most urgent disease to be ruled out is acute stroke. There was a previous report that a patient with CIN was misdiagnosed as acute stroke and hospitalized to evaluate it. Magnetic resonance imaging was performed but there were no abnormal findings. EEG showed non-convulsive status epilepticus and the patient was finally diagnosed with CIN [7]. In our case, neurologic symptoms such as cognitive impairment, aphasia, and seizure occurred after flap surgery, which is known to increase the risk of thrombus, and acute stroke was required to be excluded. Therefore, brain CT and D-dimer test were performed, but no abnormal findings were found. The triphasic morphology and slowing were observed in the EEG performed for evaluating seizure, and it was thought to be caused by metabolic causes. After cefepime was stopped and dialysis was performed, symptoms improved rapidly within 2 to 3 days, and CIN was finally diagnosed.

This case is more remarkable in that the neurologic symptoms developed and affected the surgical course in a patient who underwent flap surgery in the department of plastic surgery. The success rate of the flap varies depending on the timing of mobilization after surgery and postoperative management such as positioning and compression. Immediately after the flap, patients are usually absolutely bed rest positioned, and the compression of the flap is absolutely contraindicated as it can affect blood flow. In addition, antithrombotic agents such as aspirin and low molecular weight heparin are sometimes

used because the risk of thrombus formation increases after flap surgery [8]. This patient had seizure and delirium due to CIN after flap surgery, and compression of the flap occurred due to his movement. As a result, congestion occurred, and the pinkish flap lesion became purple in color. To improve blood flow, intralesional heparin injection and dressing with heparin gauze were performed. The patient's surgical site was completely healed after a long time.

To prevent CIN, it is a priority to identify patients with CIN risk factors such as the patient in this case. Additionally, the identification of risk factors of acute kidney injury, therapeutic drug monitoring, EEG evaluation in encephalopathy assessment, and thorough consideration of cefepime alternative antibiotics should be performed comprehensively [9].

Therefore, the authors have experienced a case of CIN after flap surgery in a patient with decreased renal function and report it as an educational case.

ORCID

Woo Jin Song, <https://orcid.org/0000-0002-8957-3950>

Chan Yeong Lee, <https://orcid.org/0000-0001-6494-8587>

Hyeong Rae Ryu, <https://orcid.org/0000-0003-0962-2407>

Je Yeon Byeon, <https://orcid.org/0000-0002-1948-0687>

Hwan Jun Choi, <https://orcid.org/0000-0002-0752-0389>

Conflicts of interest

The authors have nothing to disclose.

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