



OLGU SUNUMU/CASE REPORT

Linezolid-induced thrombocytopenia in two patients with renal dysfunction

Böbrek fonksiyon bozukluğu olan iki hastada linezolide bağlı trombositopeni

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Abstract

Linezolid is an oxazolidinone antibiotic, active against gram-positive bacteria that are resistant to other antibiotics including glycopeptides. Thrombocytopenia is an adverse effect of linezolid. Although various risk factors have been suggested, the mechanisms behind this side effect are largely unknown. Here, we report two adolescents with the diagnosis of chronic kidney disease who developed thrombocytopenia following treatment with linezolid. Our purpose in highlighting these cases is to increase the clinical awareness concerning this side effect of linezolid. While it is well known that thrombocytopenia may develop during linezolid treatment, it is relatively unknown that patients with renal dysfunction have an increased risk for the development of thrombocytopenia compared to patients without renal dysfunction.

Key words: Linezolid, thrombocytopenia, renal dysfunction

Öz

Linezolid, glikopeptidlerde dahil diğer antibiyotiklere dirençli gram pozitif bakterilere karşı etkin olan oksazolidinon grubu bir antibiyotiktir. Linezolid kullanımına bağlı görülen yan etkilerden birisi trombositopenidir. Trombositopeniye neden olan farklı birçok risk faktörü bildirilmesine karşın, bu yan etkinin nedeni tam olarak bilinmemektedir. Burada kliniğimizde kronik böbrek hastalığı tanısı ile izlenen ve linezolid tedavisi sırasında trombositopeni gelişen iki vakayı sunduk. Bu vakaları sunmaktaki amacımız linezolidin bu yan etkisi hakkında farkındalığı artırmaktır. Çünkü, linezolid tedavisi sırasında trombositopeni görülebileceği çok iyi bilinmesine karşın, bu yan etkinin gelişme riskinin böbrek fonksiyon bozukluğu olanlarda olmayanlara göre daha yüksek olduğu bilinmemektedir.

Anahtar kelimeler: Linezolid, trombositopeni, böbrek fonksiyon bozukluğu

INTRODUCTION

Linezolid (LZD) is a broad spectrum antimicrobial agent that is effective in the treatment of infections caused by multidrug-resistant Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and penicillin-resistant *Streptococcus pneumoniae*¹. The mechanism of antimicrobial action is primarily bacteriostatic, inhibiting the initiation phase of protein synthesis in microorganisms by preventing the fusion of 30S and 50S ribosomal subunits. The main side effect of LZD is reversible myelosuppression, most commonly thrombocytopenia^{1,2}. Prolonged

treatment duration, renal dysfunction, chronic liver disease, previous vancomycin use and baseline platelet count have been reported as possible risk factors for LZD-associated thrombocytopenia^{1,3-7}. Although recent studies reported that the incidence of LZD-induced thrombocytopenia was higher in patients with renal dysfunction than in patients without renal dysfunction; in clinical practice, clinicians are not aware of this adverse effect^{1,5-7}.

CASE 1

A 17-year-old male with chronic kidney disease (CKD) due to neurogenic bladder and undergoing hemodialysis attended our clinic with the complaint

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of high fever and respiratory difficulty. Physical examination on admission revealed blood pressure of 130/80 mm Hg, heart rate (HR) of 97 beats/min, temperature of 38.9 C, Respiratory Rate (RR) of 28 breaths/min and weight of 40 kg. Laboratory data on admission included blood urea nitrogen (BUN) of 60 mg/dL (normal: 5-22 mg/dL), creatinine of 8 mg/dL (normal: 0.3-1.0 mg/dL), white blood cells (WBC) of 14,800/mm³ (normal: 4,500-10,500 cells/mm³), hemoglobin of 11.5 g/dL (normal: 12.0-16.5 g/dL), and platelets of 319,000 cells/mm³ (normal: 150,000-450,000 cells/mm³). He was diagnosed with pneumonia. Empirical antibiotic therapy was started immediately with ceftriaxone. *Staphylococcus aureus* was isolated in the blood culture of patient prior to the first dose of ceftriaxone. Because the isolated microorganism was sensitive only to LZD, LZD was initiated at a dosage of 10 mg/kg three times daily. At the 17th day of LZD therapy, the platelet counts decreased from 363,000/mm³ to 85,000/mm³ progressively. Although LZD plasma concentrations were not measured in our hospital laboratory, the platelet count recovered to normal levels in our patient following the discontinuation of LZD therapy (85,000-126,000-174,000-283,000/mm³ progressively).

CASE 2

A 16-year-old female, who had CKD secondary to focal segmental glomerulosclerosis, attended our clinic with the complaint of cough and high fever. Physical examination upon admission revealed a BP of 125/80 mm Hg, HR of 122 beats/min, temperature of 39.2 C, RR of 25 breaths/min and weight of 60 kg. Laboratory data on admission included blood urea nitrogen of 40 mg/dL, creatinine of 4 mg/dL, WBC of 16,500 /mm³, hemoglobin of 6.2 g/dL and platelets of 372,000 cells/mm³.

This patient was also diagnosed with pneumonia. Empirical antibiotic therapy was started immediately with ceftriaxone. At the 5th day of empirical antibiotic therapy, meropenem and vancomycin were started as her clinical condition worsened. After the 1st week of this therapy, the patient again became febrile. Chest X-ray and CT thorax scan showed further worsening of parenchymal consolidations. As methicillin-resistant *Staphylococcus aureus* was suspected, LZD was

initiated at a dosage of 10 mg/kg three times daily. At the 16th day of LZD therapy, the platelet count decreased from 225,000/mm³ to 75,000/mm³ progressively. As such, LZD therapy was discontinued resulting in a recovery of the platelet count to normal levels (75,000-93,000-138,000-196,000/mm³ progressively).

DISCUSSION

Thrombocytopenia is defined as a platelet count of less than $100 \times 10^3/\mu\text{l}$ or a decrease of at least 50% from baseline. Several studies in the literature have investigated the risk of thrombocytopenia in patients receiving LZD therapy. Although the mechanisms of this side effect are largely unknown, it is thought to be due to reversible myelosuppression¹. Despite that a high portion of LZD is excreted via the kidney, it was reported in previous studies that the clearance of LZD is not altered in patients with renal dysfunction and that LZD concentrations in these patients were similar to those in healthy patients. Therefore, according to these studies, the dose adjustment for linezolid is not recommended for patients with renal dysfunction^{8,9}. However, the incidence of LZD-induced thrombocytopenia among patients with renal dysfunction was higher (range: 65-79%) than those in patients without renal dysfunction (range: 36-43%) (6). Renal dysfunction has been reported frequently as a risk factor of LZD-associated thrombocytopenia^{4,7}. The risk significantly increased with glomerular filtration rates $<50 \text{ mL/min/1.73 m}^2$. In addition, one study reported that pre-treatment values of creatinine clearance and blood urea nitrogen are associated with LZD-induced thrombocytopenia^{6,7,10}. In addition, it is generally considered that dose adjustment is not required for linezolid in clinical settings; the daily dose of LZD $\geq 22 \text{ mg/kg}$ was reported as a risk factor for thrombocytopenia^{10,11}. Therefore, close monitoring of platelet count and hemoglobin is recommended in patients treated with linezolid, especially in those with impaired renal function as the reduction of its clearance causes drug accumulation¹⁰. Both of our patients were taking LZD at a dose of 30 mg/kg/day.

The other factors that increase the tendency to develop of thrombocytopenia are the prolonged treatment duration (≥ 14 days) and baseline platelet count^{3,11}. Therefore, monitoring the platelet count

more than once a week is strongly recommended in patients with renal insufficiency undergoing LZD treatment for a duration greater than 2 weeks⁵. Although both of our patients had normal platelet count at the beginning of LZD treatment, the treatment duration of our patients were ≥ 14 days. We believed that this factor also affected the development of thrombocytopenia in our patients. The concomitant use of meropenem with LZD and use of vancomycin prior to LZD may worsen thrombocytopenia^{12,13}. Vancomycin was given to our second patient prior to LZD and meropenem was given concomitantly. We thought that usage of these drugs also affected the development of thrombocytopenia in our second patient. Due to this, we advise that more attention should be paid to the development of thrombocytopenia when LZD is used with other anti-infective medications as in our second case¹³.

We conclude that while linezolid is generally safe and well-tolerated, clinicians should be cautious about the potential development of thrombocytopenia in patients with renal dysfunction during linezolid treatment. Although it is well known that linezolid can cause thrombocytopenia in this type of patient, patients with renal dysfunction are not followed up by the physician for this side effect in clinical practice.

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