



Linezolid-induced Lactic Acidosis

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ABSTRACT

Lactic acidosis is a known complication of long-term linezolid therapy. We present a case where lactic acidosis developed only after 2 doses of linezolid. A review of literature revealed only 2 cases in which lactic acidosis developed soon after linezolid treatment was commenced. Both patients had underlying immunocompromising conditions. Our patient, like the previous 2 reports had an underlying immunocompromising condition - acute myeloid leukemia. It seems that linezolid has the propensity of inducing lactic acidosis soon after its commencement in immunocompromised patients.

Key Words: Linezolid, lactic acidosis, immunocompromising

INTRODUCTION

Linezolid is an oxazolidinone antibiotic active against a variety of gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Prolonged use of linezolid is associated with myelosuppression, peripheral and optic neuropathies, and serotonin syndrome. Several case reports of linezolid-induced lactic acidosis have been reported. We describe a patient with acute myeloid leukemia in whom severe lactic acidosis developed after only 2 doses of linezolid (1).

CASE

A 79-year old lady presented with increasing shortness of breath and generalized body aches of 2 weeks duration and hemoptysis of one day's duration. She was recently diagnosed with acute myeloid leukemia, when her bone marrow biopsy showed areas of marked fibrosis and

Linezolid Baęlı Gelişen Laktik Asidoz

ÖZET

Laktik asidoz uzun süreli linezolid tedavisinin bilinen bir komplikasyondur. Biz 2 doz linezolid sonrası gelişen laktik asidozlu bir olgu yu sunduk. Literatürde linezolid tedavisinden sonra kısa bir süre sonra gelişen laktik asidozlu sadece 2 olgu saptandı. Her iki hastada altta yatan immünsupresyon vardı. Bizim olguda akut miyeloid lösemiye baęlı immünsupresyon vardı. Immün sistemi baskılanmış hastalarda linezolid başlamasından sonra laktik asidoz gelişebilir.

Anahtar kelimeler: Linezolid, lactic acidosis, immünsuprese

other areas of hypercellular marrow. There was marked increase in myeloblast population, blast cell constituting 32% of the cell population. She had no other significant past medical history. She was allergic to penicillin and vancomycin. On admission she was tachypneic with respiratory rate of 26/minute and was unable to utter a full sentence. Temperature was 38°C; pulse rate 108 beats per minute and blood pressure 176/77 mmHg. Oxygen saturations were 90% on 10L of oxygen via nasal cannula. Crackles were heard throughout both lung fields. Rest of the physical examination was unremarkable. Investigations revealed white blood cell count of $134.2 \times 10^9/L$ (4.0-10.0), with eosinophilia; thrombocytopenia and blast count of $72.47 \times 10^9/L$. Hemoglobin was 100g/L (120-160). Serum sodium was 128mmol/L (135-145), potassium 4.4mol/L (3.5-5.0), anion gap 17mmol/L (10-20), urea 8.4mmol/L (3.0-7.1) and creatinine 86 $\mu\text{mol/L}$ (60-130). Alkaline phosphatase was 535 U/L (40-135), alanine aminotransferase 44U/L (4-55) and albumin 21 g/L (35-50). CTPE study showed no evidence of pulmonary

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embolism but showed bibasilar consolidation, more pronounced at the right base. Early airspace changes were seen in the right middle lobe and lingula. Brain natriuretic peptide (BNP) was 82 ng/L (<100). Arterial blood gases on 15 liters oxygen via a non-rebreather mask showed a pH of 7.38 (7.35-7.45), pCO₂ of 35mmHg (33-45) and pO₂ of 64mmHg (75-100). Blood cultures were drawn and intravenous levofloxacin and linezolid were commenced. After an initial improvement, she decompensated the following day and became extremely tachypneic and short of breath. Repeat arterial blood gases at this stage showed marked lactic acidosis. Her pH was 7.13, pCO₂ 38 mmHg and pO₂ 63 mmHg on a rebreather mask. Whole blood lactate levels were 11.1mmol/L (0.5-1.6). Serum sodium dropped to 121 mmol/L, potassium rose slightly to 5.2 mmol/L, urea and creatinine also increased to 11.5 mmol/L and 118 µmol/L respectively. More significantly, anion gap was 25 mmol/L at this stage. She had received two 600mg doses of linezolid by then.

Linezolid was discontinued and transfer to intensive care was considered. But in view of poor prognosis due to underlying leukemia, family decided to change her code status to compassionate care. She died the same evening.

DISCUSSION

Linezolid is an oxazolidinone antibiotic active against a variety of gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). It is also active against nocardia species and mycobacterium. FDA has approved linezolid for the treatment of VRE bacteremia, *E. faecalis*, nosocomial and community-acquired pneumonias caused by *S. aureus* and *Streptococcus pneumoniae*, and skin infections (1).

Prolonged use of linezolid is associated with myelosuppression, peripheral and optic neuropathies, and serotonin syndrome (2). Linezolid-induced lactic acidosis was first reported in 2003 by Apodaca et al (3). Several case reports have appeared in literature since then. In these case reports, lactic acidosis developed after several weeks use of linezolid but a few cases have been reported when lactic acidosis developed after a few days of antibiotic use. In our patient, severe lactic acidosis developed after only 2 doses of linezolid.

Type-A lactic acidosis develops as a result of tissue hypoperfusion and severe tissue hypoxia as seen in septic and

cardiogenic shocks. Type-B lactic acidosis is associated with renal and liver failures, diabetes mellitus, alcoholism, cancer, and use of certain drugs like biguanides and nucleoside reverse transcriptase inhibitors. Our patient, although septic, was not in shock and had no evidence of acute renal or liver failure. She had no history of diabetes mellitus and was not taking any medications other than linezolid associated with lactic acidosis. Although cancer (especially leukemia) might be a valid explanation for lactic acidosis, as malignant cells mainly rely on glycolysis to produce energy, normal acid base balance before the start of linezolid, temporal association of linezolid use with the development of lactic acidosis, and no other explanation for a rise in lactate levels makes linezolid the most likely cause of lactic acidosis in her case.

Linezolid inhibits bacterial protein synthesis by binding to 50S ribosomal unit (4). It is postulated that linezolid causes mitochondrial toxicity by inhibiting protein synthesis. In addition, 2 of the 3 patients with linezolid-induced lactic acidosis showed polymorphism in the mitochondrial 16S rRNA. One of these patients was found to have a homoplasmic A2706G polymorphism and the other was found to have a homoplasmic G3010A polymorphism. Same authors found A2706G polymorphism in 38% of 101 control subjects and G3010A polymorphism in 17% of 100 control subjects (5). Since A2706G and G3010A polymorphism is common in control subjects, linezolid-induced lactic acidosis would be expected to be a much more common complication than reported in the literature (6).

In most of the previously reported cases, lactic acidosis developed after prolonged use of linezolid but 2 cases have been reported where lactic acidosis developed between 4 hours and 4 days of initiation of linezolid (7,8). Both of these patients were immunosuppressed, one a recipient of liver transplant and presumably on immunosuppressive therapy and the other with a history of hepatitis-C associated cryoglobulinemia and treated with low-dose steroids. The second patient was however, treated with high dose steroids 3 weeks before for acute nephritic syndrome. Like these 2 patients, our patient was also immunosuppressed due to her acute myeloid leukemia. It therefore, seems that although linezolid-induced lactic acidosis develops after a prolonged course of antibiotic in most cases, it may develop soon after initiation of therapy in immunocompromised patients. Acid-base status should therefore, be closely monitored in patients treated with linezolid especially if they have an underlying immunocompromising condition.

In conclusion, lactic acidosis is a recognized complication of treatment with linezolid. Linezolid-induced lactic acidosis usually develops after prolonged treatment with linezolid. In immune-deficient patients lactic acidosis may develop soon after the commencement of treatment.

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