中文題目：急性骨髓性白血病患者因 Linezolid 使用導致乳酸中毒

英文題目：Linezolid-induced Lactic Acidosis in the Patient with Acute Myeloid Leukemia

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Background:

Type B lactic acidosis occurs without organ hypoperfusion and is associated with dysregulation of cellular metabolism. In hematologic malignancy, lactic acidosis might be caused by Warburg effect due to specific malignant cell metabolism. Linezolid, an oxazolidinone antibiotics, has mitochondrial toxicity and results in lactic acidosis. It's challenge for clinician to differentiate lactic acidosis in the patient with acute leukemia and prolonged linezolid used.

Method:

We reported a patient with acute myeloid leukemia in whom linezolid-induced lactic acidosis developed.

Result:

A 65-year-old woman with rheumatoid arthritis, bilateral knee joint replacement, and end stage renal disease presented with 2-days neutropenic fever caused by *Aeromonas* bacteremia. Fever subsided after cefepime treatment. Laboratory exam showed leukopenia (leukocyte count of 1,700 per cubic millimeter) with hyperblastosis (24.8%), anemia (Hemoglobin 7.4 mg/dl), and thrombocytopenia (50,000 per cubic millimeter). Acute myeloid leukemia (AML) secondary to myelodysplastic syndrome was confirmed by the results of the bone marrow biopsy. She received azacitadine and venetoclax treatment and achieved remission. Linezolid (600mg every 12 hours) was used for persistent vancomycin-resistant *enterococcus* bacteremia and bilateral knee septic arthritis. Arthrotomy and synovectomy were done to both knees without removal of the implants. The blood culture turned to negative after 11 days of treatment with linezolid. The reddish and swelling of bilateral knees were improved. Due to prolonged bacteremia and deep joint infection, we kept linezolid treatment. Three weeks later, lactic acidosis was found (80mg/dl) and persisted after hemodialysis (HD). She was transferred to intensive care unit for acute respiratory failure due to lactic acidosis related persistent severe metabolic acidosis (pH: 7.30, PCO_2 18.5mmHg, HCO^{3-} 9.1mmol/l, base deficit -17, lactate level 68

mg/dl). Because of tachycardia up to 120 beat per minutes, HD was shift to continuous renal replacement therapy (CRRT). However, the level of serum lactate still elevated. There was no evidence of shock, mesentery ischemia, or impaired liver function. After discussing with pharmacologist, we stop linezolid after 39 days of treatment and adjusted to daptomycin for the septic arthritis. The level of lactate declined to normal on the next day and CRRT was shift back to HD then (Figure 1).

Discussion

Linezolid-induced lactic acidosis is rare but potential fatal[1]. Warburg effect due to specific malignant cell metabolism might cause lactic acidosis in hematologic patients[2]. Beside the type A lactic acidosis due to tissue hypoperfusion, recognition of type B lactic acidosis is needed for clinician.

Usually, type B lactic acidosis is secondary to liver or renal failure, malignancies, and alcoholism[3]. Predominant lactic fermentation regardless of oxygen level may resulted in lactic acidosis, which is called Warburg effect. It's mostly associated with lymphoma, acute leukemia, or multiple myeloma[2]. Because of the remission of AML, Warburg effect is not likely the cause of lactic acidosis in our case.

Linezolid is an oxazolidinone antibiotics for treatment caused by methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *enterococci*, and *nocardia* species[4]. Linezolid inhibits bacterial protein synthesis by binding to 50s submit of bacterial ribosome[3]. Because of structural similarity, human mitochondrial ribosome also inhibited and resulted in mitochondrial dysfunction, which diminished global oxygen consumption and extraction and cause lactic acidosis[5,6].

Lactic acidosis due to linezolid is rare with incidence around 2.3-6.8%, and prolonged linezolid used more than 6 weeks is associated with higher risk[1]. Linezolid was metabolized by liver primarily and 30% clearance by renal excretion. Renal adjustment is not needed and ESRD is not a predisposing condition for linezolid lactic acidosis[3]. The reported mortality rate is about 25.5% in a reviewed study[7]. Although the dialysis and continuous renal replacement has showed the effect of decline of lactate level[8,9,10], discontinued linezolid is the most important treatment for the lactic acidosis.

Conclusion

Linezolid inhibits bacterial protein synthesis and may resulted in type B lactic acidosis from human mitochondrial dysfunction in prolonged linezolid use. Other than type A lactic acidosis, we should kept in mind of linezolid-induced lactic acidosis and Warburg effect in patients with AML and prolonged linezolid use.

Reference

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Figures and figures legends

Figure 1

The lactate level persistent elevation under hemodialysis and CRRT, but drop after linezolid discontinued.

In the X-axis are reported the days after linezolid starting use. The two Y-axes are the serum level of lactate and the mean arterial pressure. In the figure are also reported the day in which hemodialysis and CRRT were performed and the day on which the linezolid was discontinued.