Linezolid-Induced Lactic Acidosis: A Potentially Preventable Life-Threatening Complication

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ABSTRACT

Linezolid, an antibiotic commonly used for multi-drug-resistant (MDR) bacterial infections, inhibits bacterial protein synthesis and growth and is widely used for treating methicillin-resistant *Staphylococcus Aureus* (MRSA). Common side effects include nausea, diarrhoea, neuropathies, and bone marrow suppression. Rarely, linezolid can lead to a potentially fatal side effect of lactic acidosis (LA), the most common cause of high anion gaps metabolic acidosis (HAGMA). This report presents a case of an elderly female, who was brought to the emergency department (ED) with drowsiness as the only symptom, with severe LA found on blood work-up secondary to prolonged linezolid usage. Here, we provide an overview of the presentation and recognition of this rare adverse effect in this patient. Treating physicians should remain vigilant while prescribing such medications for longer duration with frequent monitoring for this preventable life-threatening complication.

Key Words: *Linezolid, Lactic acidosis, HAGMA, Methicillin-resistant, Staphylococcus aureus.*

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INTRODUCTION

Lactic Acidosis (LA) is generally defined as a serum lactate concentration above 4 mmol/L. It is a common cause of high anion gap metabolic acidosis (HAGMA).[1] It can be a presenting feature of a wide range of diseases, depending majorly on the precipitating cause, whether it is due to tissue hypoxia that is type A or due to deranged metabolism of lactate, or occult hypoperfusion without evidence of hypoxia which is type B. LA itself is a presenting feature of many diseases including cellular hypoxia, anaemia, seizures, and increased glycolysis (type A), or due to underlying pathology, for example, diabetic ketoacidosis, sepsis, thiamine deficiency, and toxins (type B).[2]

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major human pathogen associated with hospital and community-acquired infections. Its prevalence is increasing, accounting for almost 52% of all *Staphylococcus aureus* cases. The probable reason for this increase in antimicrobial resistance (AMR) is Pakistan's lack of proper antibiotic stewardship programmes.[3]

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Linezolid, a bacteriostatic oxazolidinone antibiotic widely used against gram-positive bacteria, is considered as an attractive choice of treatment,[4] especially for multi-drug-resistant (MDR) gram-positive cocci including MRSA, as it works primarily by inhibiting bacterial protein synthesis and growth *via* ribosomal disruption. The AMR rate is low (<1%) and is therefore used to treat resistant pathogens.[4] The pathophysiology behind LA is that it interacts with human mitochondrial ribosomes, hence leading to diminished protein synthesis and limiting aerobic energy production which therefore leads to enhanced production of lactate resulting in LA.[5] It has many side effects including nausea, diarrhoea, headache, neuropathies, and myelosuppression.[6]

To our knowledge, few case reports have been published related to linezolid-induced LA and the prevalence is reported to be 6.8% in patients on linezolid therapy. Risk factors include old age, extended use of therapy (28 days), polypharmacy, mitochondrial DNA A2706G polymorphism, and kidney or liver dysfunction.[7] Little to no data is available related to its prevalence in Pakistan. Treating physicians should remain vigilant about possible life-threatening adverse effects of antibiotics while prescribing them for a longer period.

In addition, emergency physicians should keep in view antibiotics as a possible cause of LA when dealing with patients with hyperlactataemia landing in acute settings.

CASE REPORT

A 75-year old female, with long-standing hypertension and chronic cerebral venous sinus thrombosis (CVST), was brought to the Emergency Department (ED) with complaints

of drowsiness for the past three days. Her Glasgow Coma Scale (GCS) on arrival was 6 / 15. She was normotensive, had a heart rate of 90 beats/min, an axillary temperature of 36.8°C, an oxygen saturation of 96% on room air, and a respiratory rate of 23 breaths/min.

On systemic examination, chest auscultation revealed equal air entry bilaterally. On abdominal examination, it was soft with gut sounds audible. A digital rectal examination was negative for any blood or black-coloured stool. She had pale conjunctiva raising suspicion of anaemia.

Initial work-up revealed bi-cytopenia with haemoglobin of 5 g/dl with raised mean corpuscular volume (MCV) of 100 fL, platelets of 86×10^9/l, and white blood cell (WBC) count of 10.3×10^9/l). Renal functions were deranged with a creatinine of (1.4 mg/dl), blood urea nitrogen of (66 mg/dl), and a high lactate level (18.9 mmol/l). The venous blood pH was 7.1 and pCO_2 of 21.50 mmHg confirming HAGMA secondary to raised lactate level. Electrolyte panel showed sodium levels of 145 mmol/L, chloride of 100 mmol/L, bicarbonate of 12.6 mmol/L, and phosphate level of 5.2 mmol/l revealing HAGMA. Albumin level was 3.4 g/dl. Urinary anion gap was not done. Liver function tests showed total bilirubin of 0.6 mg/dl with indirect bilirubin of 0.3 mg/dl. Serum Glutamic Pyruvic Transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT) levels were within normal limits (23 IU/L and 28 IU/L, respectively). TSH levels were 0.460 uIU/ml and cortisol levels of 63.90 ug/dl. Retic count was of 0.2%. Vitamin B12 levels were greater than 2000 pg/ml and folic acid levels were 2.31 ng/ml, respectively. Dengue antibodies and ICT malaria were negative. To rule out possible causes of high lactate levels, the work-up was extended. A nasogastric tube was placed and aspirate was negative for any possible upper gastrointestinal tract bleed. Her arterial blood gas analysis did not reveal hypoxaemia with pO_2 of 318 mmHg with O_2 saturation of 99.90%. Further possibilities were then explored. Computed tomography (CT) of the chest and abdomen with intravenous (IV) contrast was negative for pulmonary embolism and mesenteric ischaemia, respectively. During her stay in the emergency, she was transfused two packed cell volumes (PCVs) keeping in view the possible contributing factor of occult cellular hypoxia secondary to anaemia. Despite adequate IV hydration, empiric antibiotics, and concentrated bicarbonate infusion, her metabolic acidosis did not improve, and her lactic acid levels remained significantly high. Later on, her medicine history was reviewed, which revealed that she was prescribed linezolid at discharge for MRSA growth in sputum culture during her last admission. Hence, the patient had been on linezolid 600 mg twice daily since the time of discharge, taking it for almost 45 days. A provisional diagnosis of linezolid-induced LA along with myelosuppression secondary to linezolid was made. Nephrology was consulted, and an urgent session of sustained low-efficiency haemodialysis (SLED) was done, which significantly improved LA and her clinical condition. Linezolid was discontinued and supportive measures were continued, and she was admitted to the care of internal medicine services for 4 days. By discharge, her GCS had improved to 14 / 15 and her LA had fully resolved (lactic acid 2.8 mmol/l) on the day before discharge.

DISCUSSION

Cases of linezolid-induced LA have been reported after prolonged use. However, some recent studies have reported the onset of LA soon after initiation of the medicine.[8]

Management includes discontinuation of the offending agent, bicarbonate infusion, renal replacement therapy, and co-administration of cofactors for anaerobic metabolism, including thiamine l-carnitine and antioxidants.[9]

Its presentation mimics other potentially serious medical conditions including mesenteric ischaemia, hence leading to extensive diagnostic investigations and adding financial burden.

As in this case, the patient was lost to follow-up and had been using linezolid for almost 45 days without any regular monitoring of the lactate levels, blood gases, and electrolytes, which led to this critical life-threatening situation. She went through extensive work-up and radiation exposure to look for possible causes of LA, hence, not only adding financial burden but also the health hazards related to radiation exposure. Eventually, the patient went through a dialysis session *via* a double-lumen catheter, adding another possible site for infection as supported by the study done by Ferreira *et al*., which showed that 10.4% of patients had an infection at the catheter site, 14.3% had blood stream infections related to catheter and microbiological colonisation was found in 51% of the patients who underwent temporary double-lumen catheter placement for haemodialysis.[10] This could have been an easily preventable situation if regular checks and balances had been kept during this prolonged linezolid therapy.

We aim to encourage healthcare providers to be vigilant when prescribing linezolid, especially in elderly patients with comorbidities, considering potential life-threatening adverse effects and the regular monitoring for the development of LA throughout treatment to avoid such complications.

In conclusion, LA is a potentially life-threatening side effect of linezolid and needs vigilant monitoring. Treating primary physicians should do periodic monitoring with regular lactate levels and blood gases keeping in view the possible risk factors leading to these complications. In addition, emergency physicians should remain on high alert when dealing with LA and should keep medicines as a possible differential for hyperlactataemia. As the usage of linezolid has been increasing due to antibiotic resistance, further research is required in this field, especially in Pakistan, for a better understanding of the medicine, its adverse effects, and its prevalence.

PATIEN'S CONSENT:

Written informed consent was obtained from the guardian of the patient for the publication of this study.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

QAA, SA: Formulated the manuscript and gathered relevant information.

ZA: Obtained consent and gathered information, formulated the manuscript, and prepared.

SW: Gave intellectual input and proof read the manuscript.

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