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Linezolid-Induced Cardiac Arrest in an Adolescent: A Case Report

Medhagopal R. G. [1], Saroj K. Tripathy [1], Sarthak Das [1], Archana Malik [2]

1. Pediatrics, All India Institute of Medical Sciences, Deoghar, Deoghar, IND 2. Pulmonary Medicine, All India Institute of Medical Sciences, Deoghar, Deoghar, IND

Corresponding author: Sarthak Das, sarthak.ped@aiimsdeoghar.edu.in

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Abstract

Drug-induced cardiovascular adverse effects can result in significant morbidity and mortality. Although linezolid, a synthetic oxazolidinone effective against resistant gram-positive infections, has well-recognized side effects, cardiac rhythm disturbances have been rarely reported. We describe the case of a 14-year-old boy with mixed sleep apnea requiring prolonged mechanical ventilation who developed bradycardia and cardiac arrest following initiation of linezolid for methicillin-resistant *Staphylococcus aureus* infection. Episodes of sinus bradycardia and cardiac arrest occurred temporally after linezolid infusion and resolved upon discontinuation, with no recurrence on alternative therapy. Other metabolic, drug-related, or reversible causes were excluded. Based on Naranjo's scale, the adverse reaction was classified as probable. This case emphasizes the importance of vigilant cardiovascular monitoring during linezolid therapy, as rare but life-threatening bradyarrhythmias may occur.

Categories: Family/General Practice, Cardiology, Emergency Medicine
Keywords: adverse drug reaction, bradycardia, cardiac arrest, linezolid, methicillin-resistant staphylococcus aureus (mrsa)

Introduction

Cardiovascular effects of drugs are a potential cause of life-threatening morbidity and mortality in patients. The toxicity of drugs includes rhythm disturbances, myocardial ischemia, cardiac dysfunction, and changes in the vascular system (embolism, hypertension, and hypotension) [1]. Commonly used drugs like digoxin, calcium channel blockers, beta blockers, tricyclic antidepressants, lithium, and opioids are known to cause bradycardia [2].

Linezolid is a synthetic oxazolidinone antimicrobial used for gram-positive infections, with its adverse effects being well known [3]. However, bradycardia and cardiac arrest associated with linezolid therapy are not substantiated in the literature. Here we report the case of an adolescent who developed sinus bradycardia and cardiac arrest following administration of linezolid. This case highlights a rare but potentially life-threatening cardiovascular adverse effect of linezolid and emphasizes the importance of cardiovascular monitoring during therapy.

Case Presentation

A 14-year-old boy presented to our hospital with complaints of multiple nocturnal awakenings associated with headache, excessive daytime sleepiness, and poor scholastic performance for six months. Parents also noticed increased frequency of urination at night associated with primary nocturnal enuresis. Antenatal, natal, and postnatal periods were uneventful.

On examination, the patient was irritable, overweight, with stable vitals, and systemic examination was normal. Capillary blood glucose was 84 mg/dl. Blood gas showed respiratory acidosis with a high partial pressure of carbon dioxide (pCO2) (95 mmHg). He was admitted, and polysomnography revealed mixed apnea. Continuous positive airway pressure (CPAP) therapy was initiated with titration. However, he did not tolerate CPAP and developed severe hypercapnia and respiratory failure. Blood gas showed respiratory acidosis (pH: 6.84, partial pressure of oxygen (pO2): 116.7 mmHg, pCO2: 277.2 mmHg, bicarbonate (HCO3): 46 mEq/L).

On day 2 of admission, the patient was intubated, and mechanical ventilation was started in view of type 2 respiratory failure. He failed the extubation trial multiple times, requiring prolonged ventilation. On day 10 of mechanical ventilation, tracheostomy was done in view of needing prolonged ventilator support.

On day 30 of admission, he developed a hospital-acquired infection. Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated from both blood and urine cultures. Hence, linezolid was started based on the antibiogram and was infused at a dose of 10 mg/kg/dose every eight hours under continuous monitoring. On day 3 of linezolid infusion, just after completion of medication, the patient developed sudden bradycardia

and cardiac arrest, which was reversed successfully with cardiopulmonary resuscitation (CPR) for three minutes and one dose of adrenaline within two minutes. Other potential reversible causes of bradycardia and cardiac arrest were ruled out. ECG showed sinus bradycardia (Figure *1*).

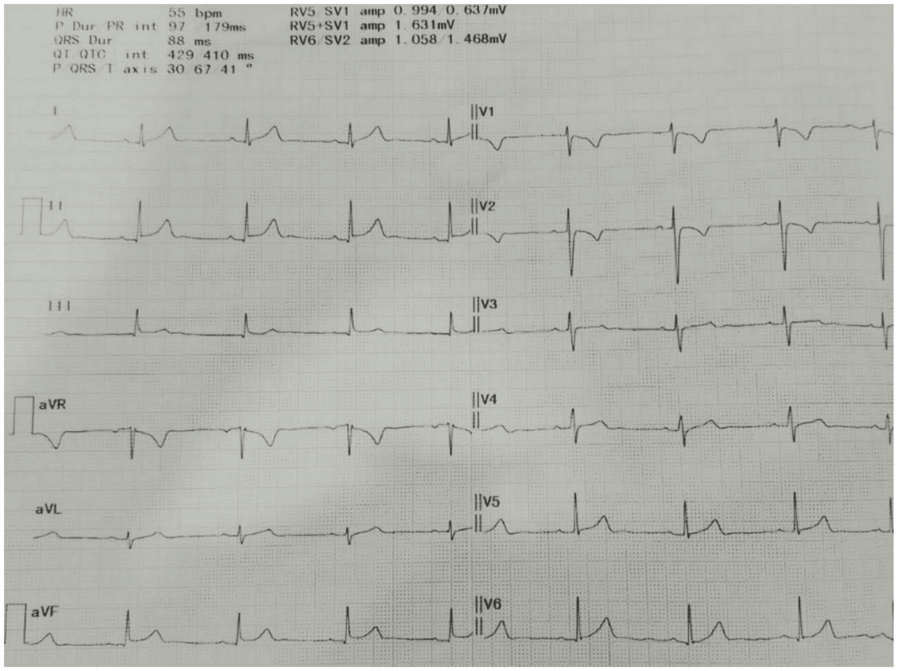


FIGURE 1: ECG showing sinus bradycardia following linezolid administration

Laboratory test results are given in Table *1*.

Parameters		Patient value	Reference value
Hemogram	Haemoglobin (g/dL)	8.3	11 – 15.5
	Total leucocyte count (10^3/microL)	11,630	4 – 11
Differential lymphocyte count (%)	Neutrophil	60	40 – 75
	Lymphocyte	30	20 – 45
	Monocyte	6	2 – 10
	Eosinophil	4	0 – 6
	Basophil	0	0 – 1
Renal Function Test	Urea (mg/dL)	13	10 - 45
	Creatinine (mg/dL)	0.19	0.2 – 1.2
	Sodium (mmol/L)	131	135 – 145
	Potassium (mmol/L)	4.4	3.5 – 5
	Calcium (mg/dL)	9.9	8.6 – 10.3
Liver Function Test	Bilirubin Total (mg/dL)	0.5	0.1-1.2
	Bilirubin Direct (mg/dL)	0.2	0.1 – 0.3
	Alanine transaminase (U/L)	12	0 - 31
	Aspartate aminotransferase (U/L)	18	5 - 34
	Total protein (g/dL)	6	6.5 – 8.3
	Serum Albumin (g/dL)	3.6	3.5 - 5
	Capillary blood sugar (mg/dL)	118	
	C-reactive protein (mg/L)	12	< 5
Arterial Blood Gas	pH	7.44	-
	pO2 (mm Hg)	74.4	-
	pCO2 (mmHg)	53.9	-
	HCO3 (mEq/L)	36	-
	Sodium (mmol/L)	130	-
	Potassium (mmol/L)	3.3	-

TABLE 1: Laboratory test results

pO2: partial pressure of oxygen; pCO2: partial pressure of carbon dioxide; HCO3: bicarbonate

The patient was on pressure support ventilation and not on any sedatives or other drugs. Since no cause was found, the same line of management was continued, and vitals were monitored keenly. Forty-eight hours later, the patient again developed bradycardia and unresponsiveness. This time, he needed 15 minutes of CPR for revival and return of sinus rhythm. The possibility of an adverse reaction to linezolid, causing bradycardia and cardiac arrest, was considered, and linezolid was withdrawn. Intravenous teicoplanin was substituted in place of linezolid and was continued for 10 days.

The patient did not have any alteration in blood pressure during linezolid therapy except at the time of cardiac arrest. Linezolid was not reintroduced to confirm the effect due to the possibility of the occurrence of life-threatening complications. He did not develop any further episodes of bradycardia or cardiac arrest during hospitalization. He was successfully extubated and discharged with intermittent bilevel positive airway pressure (BiPAP) therapy.

The Naranjo adverse drug reaction probability scale was used to assess the likelihood that the observed adverse drug reaction was related to the drug administered [4]. The parameters considered included previous reports of similar reactions (+1), the appearance of the reaction after administration of the suspected drug (+2), improvement after discontinuation of the drug or administration of a specific antagonist (+1), the presence of other possible causes for the reaction (+2), recurrence of the reaction after placebo administration (+1), and confirmation of the reaction by objective evidence (+1). Thus, adverse reaction was calculated as "probable" with a score of 8.

Discussion

Linezolid is a synthetic oxazolidinone antimicrobial drug. It inhibits the protein synthesis of bacteria by interfering with translation. This drug inhibits bacterial protein synthesis by binding to the bacterial 23S ribosomal RNA of the 50S subunit, thereby interfering with the assembly of a functional 70S initiation complex. Nearly 30% of the drug is excreted unchanged in urine as the parent drug and 50% as metabolites; the rest is reabsorbed by the renal tubules. It is indicated against gram-positive organisms, mainly enterococci, skin and soft tissue infections, and pneumonia, where methicillin- or vancomycin-resistant *Staphylococcus* is suspected. Adverse effects of this drug include headache, vomiting, nausea, hypertension, myelosuppression (anemia, thrombocytopenia), and, in the case of prolonged use, *Clostridium difficile*-associated diarrhea and pseudomembranous colitis [3].

Linezolid use has the possibility of lactic acidosis, neuropathy, and hyponatremia in high-risk patients [5]. Cardiac effects of linezolid, such as QT prolongation and torsades de pointes, are uncommon adverse effects mostly observed in older adults and patients with preexisting heart diseases. Linezolid is a reversible monoamine oxidase (MAO) inhibitor that can release neurotransmitters like epinephrine, norepinephrine, and serotonin. Tachycardia following linezolid use has been attributed to serotonin syndrome occurring as an adverse effect of the drug [6].

Bradycardia and cardiac arrest are rare and poorly understood side effects. An extensive search of the literature reveals that only two case reports are available. Tartarone et al. published a case of a 49-year-old woman with fever and malignant jaundice developing bradycardia and hypertension following linezolid therapy, underscoring the possibility of a drug-induced phenomenon [7]. Song et al. reported this adverse effect in a 13-day-old neonate who received linezolid for MRSA infection. Still, the baby succumbed to death following a hypoxic insult caused by post-cardio-respiratory resuscitation [8]. Fortunately, in our case, the patient was revived. The patient did not have any other metabolic or electrolyte abnormalities or any other potential drug interactions. Our case was unique because it did not have hypertension or other adverse effects except bradycardia, and it was successfully resolved with discontinuation. This report highlights a rare but life-threatening complication of linezolid.

Conclusions

Given widespread use of linezolid among inpatients, clinicians should be aware of the potential life-threatening adverse effects. This case highlights the importance of vigilant monitoring of vitals while administering medications to lessen risks and ensure patient safety. Baseline heart rate, ECG, and metabolic panel are helpful in crisis management. Further research is needed to confirm the causal relationship and to explore the underlying mechanism.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Sarthak Das, Saroj K. Tripathy, Medhagopal R. G., Archana Malik

Critical review of the manuscript for important intellectual content: Sarthak Das, Saroj K. Tripathy, Archana Malik

Supervision: Sarthak Das

Acquisition, analysis, or interpretation of data: Saroj K. Tripathy, Medhagopal R. G.

Drafting of the manuscript: Medhagopal R. G.

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