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LINEZOLID-INDUCED PANCREATITIS ASSOCIATED WITH LACTIC ACIDOSIS AND RELATIVE HYPOGLYCEMIA: A RARE CASE REPORT

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ABSTRACT

Background: Linezolid is known to cause side effects, including nausea, diarrhea, and headaches of short duration. As extended use of linezolid is becoming more common, additional rare side effects should be considered.

Case Presentation: A 68-year-old man hospitalized for osteomyelitis developed severe abdominal pain and altered mental status following five weeks of linezolid therapy. Laboratory studies showed very high lipase levels, lactic acidosis not responding to resuscitation, and relative hypoglycemia. All common causes of pancreatitis were ruled out, and a trial of linezolid withdrawal was done resulting in drastic improvement in the patient's clinical status.

Conclusions: For patients on extended course of linezolid who develop abdominal pain, drug-induced pancreatitis should be considered as a side effect, and a trial of withdrawal of linezolid should be undertaken.

KEYWORDS

Drug-induced pancreatitis, acute pancreatitis, linezolid side effect

LEARNING POINTS

- Linezolid can be associated with a rare but serious triad of adverse effects of pancreatitis, hypoglycemia, and lactic acidosis.
- Possible risk factors include a prolonged course of linezolid, renal dysfunction, and sepsis.

INTRODUCTION

Linezolid is a synthetic antibiotic of the oxazolidinone class used to treat Gram-positive infections, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*[1]. It is primarily used as an alternative to vancomycin for infections such as pneumonia, skin and skin structure infections, and meningitis[1]. Common adverse effects include headaches, rash, gastrointestinal disturbances, peripheral neuropathy, hyperlactatemia, hypoglycemia, anemia and thrombocytopenia[1]. Additionally, there have been reports of a triad of hypoglycemia, hyperlactatemia, and pancreatitis associated with linezolid

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use[2,3]. Here we describe a case of pancreatitis linked to linezolid use.

CASE REPORT

We present a case report of a 68-year-old male with a history of heavy smoking, hypertension, type 2 diabetes mellitus with neuropathy, chronic kidney disease, and chronic diabetic foot infections for one year. He was bed bound, oral feeding, basically communicative. He was admitted with a two-day history of decreased responsiveness. Initial diagnosis was sepsis due to osteomyelitis in his left foot. Wound culture showed *Pseudomonas aeruginosa*, *Escherichia coli*, and *Enterococcus faecium*, and based on sensitivities, he was started on oral linezolid 600 mg for 6 weeks and IV cefepime 2 g every six hours for 2 weeks. The patient improved completely after a few days, but he remained hospitalized due to social issues.

One month into admission, the patient developed severe abdominal pain and a drop in consciousness. Arterial blood gas showed respiratory acidosis requiring non-invasive ventilation. Laboratory studies revealed lipase levels >3000 U/l, lactate levels ranging between 3 - 4 mmol/l, and relative hypoglycemia ranging between 3.4 - 4.9 mmol/l. Other laboratory tests were unremarkable. The patient had no previous history of pancreatitis or family history of pancreatitis, and ultrasound showed no evidence of common bile duct calculus or dilatation. The patient also had platelet levels that were dropping within the normal range at the start of linezolid treatment and eventually reached a nadir of 46 x 10^3/µl (normal: 150 – 450 x 10^3/µl) but started to increase back to the normal range three days after linezolid treatment was discontinued. Given the lack of an obvious cause of pancreatitis and persistently high lactate levels, linezolid was suspected to be the cause of the symptoms based on previous case reports. The patient was switched to daptomycin three days after developing pancreatitis.

After linezolid was stopped, the patient's abdominal pain improved, lipase levels decreased, lactate levels started trending down, and his overall condition started to improve. However, before the patient was fit to be discharged, due to prolonged stay in the hospital and multi-morbidity, he deteriorated again with other hospital-acquired infections, fluid overload, and progression of his kidney disease. The patient passed away from septic shock six months after the episode of pancreatitis.

DISCUSSION

Linezolid as an antibacterial drug is metabolized into two inactive metabolites: hydroxy ethylene glycine and aminoethoxy acetate hepatically, which are then cleared by the kidney[1]. Patients with renal failure tend to accumulate these metabolites in their bodies, but it remains difficult to determine which metabolite is responsible for the drug's toxicity[1]. Our patient's severe renal dysfunction requiring hemodialysis during this hospital course may have contributed to lower clearance of the drug metabolites, increasing his risk of developing toxic effects from linezolid.

Linezolid may induce pancreatitis by causing microcirculatory disturbances due to mitochondrial dysfunction, leading to inflammation and necrosis of the pancreatic tissue. It may also cause direct injury to the pancreatic acinar cells, leading to pancreatitis[3].

The proposed mechanism for linezolid-induced hypoglycemia pertains to the inhibition of catecholamine uptake by the adrenal medulla, leading to reduced glucagon secretion and impaired hepatic gluconeogenesis. Additionally, linezolid has been shown to impair mitochondrial function and oxidative phosphorylation, which can also contribute to hypoglycemia by reducing ATP production in the liver[2]. The exact mechanism, however, remains unclear and further studies are needed to elucidate it.

Linezolid-induced pancreatitis is a rare adverse effect, with limited cases reported in the literature. Tobias et al. reported on a case with small bowel resection, while Johnson et al. reported on a case with end-stage renal disease. Both cases featured the triad of pancreatitis, hypoglycemia, and lactic acidosis with linezolid use[2,3]. Moreover, in a review article by Rose et al., a case of severe pancreatitis and lactic acidosis was reported in a child with drug-resistant tuberculosis after six months of linezolid use[4]. A systematic review for drug-induced pancreatitis reported linezolid in class IV, which means that at least one case of pancreatitis associated with linezolid was reported in the literature, but this study did not include a positive challenge test nor ruled out other causes[5]. Despite the fact that our patient deteriorated in his later hospital course, there was clear evidence clinically and from his laboratory results that his pancreatitis improved after removal of linezolid. All other common causes were ruled out, including other medications, thus his Naranjo score (adverse drug reaction probability scale) was seven, indicating a probable association between the drug and adverse effects[6].

CONCLUSION

This case report highlights a rare but potentially serious adverse effect of linezolid, which is the induction of pancreatitis, hypoglycemia, lactic acidosis, and thrombocytopenia. Although there are limited data on this adverse effect, it is important for clinicians to be aware of it, especially in patients receiving prolonged courses of linezolid and those with comorbidities such as renal failure and sepsis. The exact mechanism of this side effect remains unclear, but it could be related to the penetration of linezolid in the pancreatic tissue. Withdrawal of the drug is usually sufficient for improvement, but in severe cases, additional treatments such as hemodialysis may be necessary. Further research is needed to better understand the risk factors, pathophysiology, and optimal management of this rare but potentially serious adverse effect.

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