Published in final edited form as:
Pediatr Infect Dis J. 2011 September ; 30(9): 804–806. doi:10.1097/INF.0b013e3182186035.

Linezolid and Lactic Acidosis: A Role for Lactate Monitoring With Long-term Linezolid Use in Children

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Abstract

Linezolid administration has been associated with lactic acidosis in adults; however, the same phenomenon has not been reported in children. Mitochondrial protein synthesis inhibition is a demonstrated mechanism for toxicity, which therefore may manifest as lactic acidosis. Three cases of linezolid associated lactic acidosis in children are reported to reinforce the need for pediatric caregivers to be vigilant of this potential side effect.

Keywords

pediatric; lactic acidosis; linezolid; vancomycin resistant enterococcus; multidrug resistance; mitochondria

Introduction

Linezolid, an oxazolidinone antibiotic, is useful against multidrug resistant Gram-positive bacteria by virtue of its unique suppression of mRNA translation in prokaryotic organisms. In particular it is an agent of choice against vancomycin-resistant *Enterococcus faecium* (VRE). Several adult case reports describe lactic acidosis as an adverse effect of linezolid[1–3]. A putative cause of toxicity is inhibition of mitochondrial protein synthesis as demonstrated in cell models of linezolid exposure[4–6]. Possible reasons are physiologic homologies mitochondria share with prokaryotes. Given that lactate catabolism occurs primarily in the liver and kidneys, dysfunction of these organs could place a patient at risk for linezolid induced lactic acidosis. To date, this adverse effect has not been reported in children regardless of hepatic or renal status. This communication presents experiences with three pediatric patients who received courses of linezolid complicated by lactic acidosis. This highlights the need for caregivers to be vigilant for its development.

Case 1

A 6 month-old boy with a history of prematurity at 25 weeks was admitted for small bowel and liver transplantation evaluation due to previous necrotizing enterocolitis and liver disease with coagulopathy. His medical history included polymicrobial peritonitis, methicillin-resistant *Staphylococcus aureus* (MRSA), VRE, and ventilator dependent

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bronchopulmonary dysplasia. During his admission he had multiple infections including respiratory tract *Citrobacter*, *Enterobacter* and MRSA for which he was treated. Early in his admission he received linezolid for surgical site MRSA following repair of mucocutaneous fistulas and a history of VRE. After four days of therapy he demonstrated no culture positivity or clinical signs of acidosis. Four weeks later an ESBL-producing *K. pneumoniae* catheter associated bloodstream infection necessitated ciprofloxacin and amikacin treatment that continued until 10 days after cultures cleared. However, he concomitantly developed a VRE bloodstream infection which was treated with linezolid for 14-days. Cultures became negative, but a progressive metabolic acidosis developed with a pH of 7.37 on day 1 of therapy trending to 7.13 on day 13, lactate level measured at 4.9mEq/L (reference ranges 0.5–1.3 mEq/L) on day 13. Linezolid was discontinued as planned and his acidosis resolved.

As a diagnosis of linezolid associated lactic acidosis was not clear, a third course of linezolid was administered 3 weeks later to treat sepsis symptoms and confirmed tracheal VRE. Coagulopathy from hepatic insufficiency led to unremitting slow mucosal bleeding, and plasma exchange was performed for multiple system organ failure. Despite exchange, his lactate level peaked at 6.1mEq/L. He remained symptomatic from recalcitrant VRE. At 39 days after linezolid was started for his airway cultures, the patient clinically worsened with pressor-refractory shock and his lactate levels abruptly rose to 24mEq/L. Linezolid therapy was discontinued and despite aggressive supportive care including continuous renal replacement therapy (CRRT), the lactic acidosis improved only marginally and he died two days later.

This patient received four separate courses of linezolid totaling 53 days of treatment.

Case 2

A 6 month-old female with hepatic insufficiency and failure to thrive was admitted for a gastroenterology evaluation. She was mechanically ventilated from arrival for persistent respiratory failure. She had protein-losing enteropathy with resultant hypogammaglobulinemia, hyponatremia, and chronic diarrhea. Her bloody stools and persistent protein losses resulted in hypoalbuminemia with interstitial fluid accumulation. Diuresis, octreotide, and albumin supplementation were provided for maintenance of her tenuous state. Early in her stay her lactate remained in the range of 0.9–1.6 mEq/L. This was in light of significant inotropic support and adrenal replacement therapy. Eight weeks into her hospital stay linezolid was added empirically because of prior VRE infection and suspected sepsis. Linezolid was continued when VRE grew from a respiratory specimen. Subsequently she was diagnosed with congenital disorders of glycosylation Type 1A both by serology and skin biopsy.

Four weeks after linezolid initiation she had significant metabolic acidosis and was found to have a serum lactate of 7.9 mEq/L. In the last week of her life her multiple organ system failure worsened and despite increasing cardiovascular support her serum lactate levels did not improve. Her oxygenation deteriorated and her lactates climbed as high as 38.1 mEq/L. She manifested refractory hypotension and died soon after.

Her lactate value was 2.4 mEq/L and elevated ten days after starting linezolid. It rose to 7.9 mEq/L with the development of metabolic acidosis 27 days into linezolid therapy. D-lactate at 29 days into treatment was not detected with a concomitant whole blood lactate of 13.2 mEq/L, indicating that her hyperlactatemia was likely not from intestinal sources. Cumulatively she received 31 days of linezolid.

Case 3

A 16-year-old male with cryptogenic cirrhosis was admitted for poor weight gain and refractory ascites. A venogram demonstrated bilateral hepatic vein occlusion, and portal hypertension was documented with asymptomatic esophageal varices. His ascites was symptomatic and frequently required drainage during admission. He transiently required broad spectrum antimicrobial coverage for spontaneous bacterial peritonitis (SBP) but was otherwise maintained on SBP prophylaxis. In his first month of admission he developed *Candida* peritonitis with a MRSA bloodstream infection. These were treated with liposomal amphotericin B and vancomycin respectively. He developed *Clostridium difficile* enteritis and *Enterobacter cloacae* peritonitis with resultant abdominal distention and respiratory insufficiency. Ongoing supportive management included intermittent drainage, diuretics, octreotide, directed antibiotic therapy, and mechanical ventilation.

During the next month of his stay he had a period of relative stability, and underwent hepatic vein dilatation and stent placement. Approximately a week later he developed depressed mental status and worsening respiratory distress. Linezolid was started for VRE in his urine with antifungal and broad-spectrum peritoneal coverage. His lactate concentration at this time was 0.9 mEq/L. He was soon intubated for worsening respiratory status and required inotropic support. By day six of linezolid therapy his lactate level had increased to 8.7 mEq/L as he developed pressor-refractory shock. Despite CRRT, his lactate concentration continued to rise being 28 mEq/L by day seven of linezolid therapy. Given his rapidly deteriorating status his family withdrew support.

Discussion

Linezolid is one of few antimicrobials available for multidrug resistant Gram-positive bacterial infections. Alternatives include daptomycin, quinupristin/dalfopristin, doxycycline and chloramphenicol, but linezolid has a comparatively low adverse effect profile, and an oral formulation. Current approved indications for linezolid include treatment of VRE bacteremia, *Enterococcus faecalis*, nosocomial and community-acquired pneumonias caused by *Staphylococcus aureus* or *Streptococcus pneumoniae*, and skin infections.

Lactic acidosis has emerged as a rare but significant adverse effect of linezolid in adults[7]. Apodaca and Rakita[1] in 2003 first described reversible lactic acidosis in a patient who received 11 weeks of linezolid for a *Nocardia* pneumonia. The patient's lactate peaked at 9.9 mMol/L but normalized in two weeks following cessation of linezolid. Subsequently Palenzuela and colleagues[2] described three patients who developed lactic acidosis after receiving extended courses of linezolid (40 – 84 days) with lactate values between 9.9 and 18.4mMol/L. The investigators also noted mutations in the mitochondrial 16S rRNA in two individuals. Notably, bacterial 23S rRNA binds linezolid in cross-linking studies and shares conserved sequences with mammalian mitochondrial 16S rRNA, supporting the mechanism of linezolid-induced lactic acidosis as being likely related to structural homology between bacterial and mammalian mitochondrial rRNA.

A patient with liver dysfunction after receipt of a liver transplant has been noted to develop lactic acidosis within the first week of treatment as opposed to longer courses[4]. The authors hypothesized that hepatic insufficiency increased the risk for hyperlactemia and likewise parallels Case 3 in the current communication. Hepatic dysfunction has also been implicated in thrombocytopenia development while receiving linezolid, another adverse effect of long-term administration[8]. Moreover, renal insufficiency has also been implicated in delayed linezolid clearance[9], and may have influenced toxicity onset in our patients as all had elevated serum creatinine. Consistent with cases involving hepatic dysfunction, the patients

described in the current series demonstrated onset of delayed hyperlactatemia with late, rapid escalation. This may reflect either a threshold at which mitochondrial inhibition causes aerobic metabolic failure, or when lactate production overwhelms its consumption. Of note, evidence exists suggesting linezolid impairs its own clearance over time[10], possibly potentiating toxicity during prolonged courses.

In 2005 Soriano et al.[5] found patients with linezolid-associated lactic acidosis to have depressed mitochondrial complex IV activity. The authors suggested that this reflects mitochondrial mRNA translation interference. This contrasted with relatively preserved function of complex II, which is encoded on nuclear DNA. This group further demonstrated that patients who developed lactic acidosis also had 51% of the respiratory chain activity seen in controls, lower mitochondrial mass, and decreased cytochrome c oxidase subunit II (COX-II) protein expression without a concomitant decrease in mitochondrial DNA content. COX-II function recovered after withdrawal of linezolid[6].

The precautions section of the linezolid commercial package insert states that patients experience “repeated episodes of nausea and vomiting,” when developing lactic acidosis. These did not occur in all of the cases noted in the literature, nor in the cases described here. Since pediatric patients may not express nausea clearly, it is prudent to follow lactate concentrations in pediatric patients receiving prolonged courses of linezolid or who have underlying hepatic or renal dysfunction. Future investigation is warranted into whether linezolid-related adverse phenomena such as lactic acidosis are associated with lower linezolid clearance in the setting of hepatic or renal dysfunction. This may include monitoring linezolid concentrations. This is of interest because linezolid dosage is not adjusted for patient hepatic or renal function.

Acknowledgments

Support: This work was supported in part by T32HD040686

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Table 1

Summary of cases

							Parameters near lactate peak					
Age/gender	**Underlying Diagnosis**	**Pathogen treated**	**Infection site**	**Dose**	**Course**	**Lactate peak**	**Lowest pre-transfusion Platelets**	**Lowest pre-transfusion Hgb**	**Bilirubin**	**AST**	**ALT**	**Creatinine**
Case 1 6m/male	Short bowel syndrome	VRE	Respiratory, bloodstream	75mg (10mg/kg) q8h	39 days	24.0 mMol/L	27×10^9/L	8.1g/dl	28.5 mg/dl	2,617 IU/L	685 IU/L	1.1 mg/dl
Case 2 6m/female	CDG-1A	VRE	Respiratory	47mg (10mg/kg) q8h	31 days	38.1 mMol/L	60×10^9/L	7.9g/dl	0.7 mg/dl	205 IU/L	101 IU/L	0.8 mg/dl
Case 3 16y/male	Cryptogenic cirrhosis	VRE	Urinary tract	600mg (18mg/kg) q12h	7 days	30.0 mMol/L	44×10^9/L	7.3 g/dl	35.5 mg/dl	2,749 IU/L	357 IU/L	2.6 mg/dl

VRE: Vancomycin-resistant enterococcus CDG-1A: Congenital Disorders of Glycosylation Type 1A