Severe Linezolid Associated Lactic Acidosis Temporized by CRRT

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Introduction

Linezolid is an oxazolidinone antimicrobial used increasingly in hospitals for gram positive bacterial infections, especially Vancomycin Resistant Enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA) infections.[1]

It is a ribosomal inhibitor which blocks the fusion of 30S and 50S ribosomal subunits, preventing protein synthesis in bacteria as well as in human mitochondria. With prolonged use this interferes with mitochondrial respiratory chain activity, leading to lactate accumulation.[2]

We report a case of chronic linezolid use for VRE infection causing mild, subtle chronic lactic acidosis in a 78-year-old female post colectomy, resulting in catastrophic lactate acidosis following a 2nd abdominal surgery. The severe acidosis was successfully temporized by CRRT (continuous renal replacement therapy), with lactate levels slowly improving nine days after linezolid withdrawal.

Anion Gap (AG) calculation

As this patient experienced a prolonged illness and was hypoalbuminemic before and during linezolid use, we calculated a corrected anion gap adjusting for hypoalbuminemia.[3]

This equates to adding 2.5 to the observed anion gap for every gram the albumin is below 4.

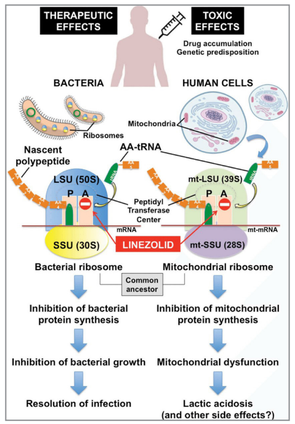

Figure 1. Santini, Alessandro & Ronchi, Dario & Garbellini, Manuela & Piga, Daniela & Protti, Alessandro. (2017). Linezolid-induced lactic acidosis: the thin line between bacterial and mitochondrial ribosomes. Expert opinion on drug safety. 16. 10.1080/14740338.2017.1335305.

Case

A 78-year-old female underwent colon resection, ostomy creation, and abscess drainage after sigmoid diverticulitis rupture. Tissue cultures grew VRE. Linezolid 600 mg twice daily was initiated and she left the hospital for outpatient follow up. Six days after discharge, she presented with abdominal pain and hypotension. Another retroperitoneal abscess was discovered despite the linezolid use along with an anion gap (AG, corrected for hypoalbuminemia) acidosis of 16 and venous lactate of 5.3 mmol/L. Her serum lactate, serum bicarbonate, and hypotension improved with IV fluids and blood pressure improvement. However, her AG persisted – despite a low normal serum bicarbonate level – and linezolid was continued.

She remained on linezolid for 32 days, until she underwent a second surgery for ostomy revision and abscess drainage. Immediately postoperative, hypotension and severe acidosis developed: pH 6.9 (AG corrected for hypoalbuminemia was 24). Her venous lactate was 12.5 mmol/L and arterial lactate rose as high as 16 mmol/L. Both venous and arterial lactate levels were followed to check concordance of values. After RBC transfusion and fluid resuscitation, her hemodynamics improved. She remained acidotic.

Subsequently, IV NaHCO3 (10 mEq/hr) was initiated. Linezolid was discontinued. After 8 hours of IV NaHCO3, her pH remained 7.19 with venous lactate of 14.4 mmol/L, despite systolic pressures in the 120s, urine output of 75 ml/hr, and normal LFTs (suggesting adequate organ perfusion.) Furthermore, the patient's thiamine levels were normal which ruled out thiamine-deficiency associated Type B acidosis.[4] With evidence of adequate organ perfusion, we interpreted the continuing lactic acidosis as due to mitochondrial dysfunction. CVVHDF (continuous venovenous hemodiafiltration) was initiated with aggressive NaHCO3 replacement (dialysate NaHCO 32 mEq/L and replacement NaHCO3 75 mEq/hour for 4 hours). Her pH improved to 7.28 and CRRT was adjusted to standard dialysate (32 mEq NaHCO3/ L /hour), and standard replacement solution (32 mEq bicarbonate/L @ 1.5 L/hour= NaHCO3 replacement of 48 mEq/ hour).

Both the dialysate and replacement solutions contained 32 mEq bicarbonate/L, and sodium lactate 3 mEq/L. During her illness the serum lactate levels were well above the lactate concentration of the CVVHDF solutions, but we could not discount a small contribution to the inability of the mitochondrial dysfunction to convert the CVVHDF small lactate load to bicarbonate during treatment.

CRRT was discontinued five days later when serum pH was 7.38, with a venous lactate at 7.9 mmol/L. IV D5W + 150mEq sodium bicarbonate was required thereafter. She remained normotensive yet serum lactate normalized nine days after linezolid discontinuation. The patient elected to pursue comfort care given her multiple surgical complications and expired.

Results

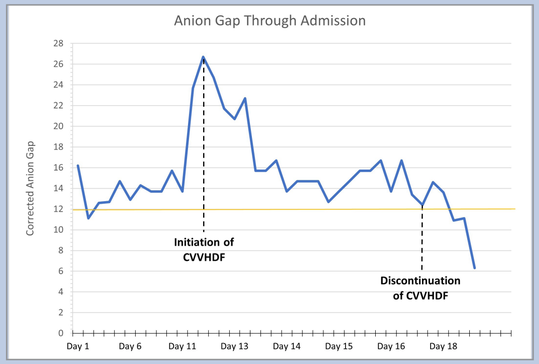

Figure 2. Anion gap corrected for hypoalbuminemia throughout admission.

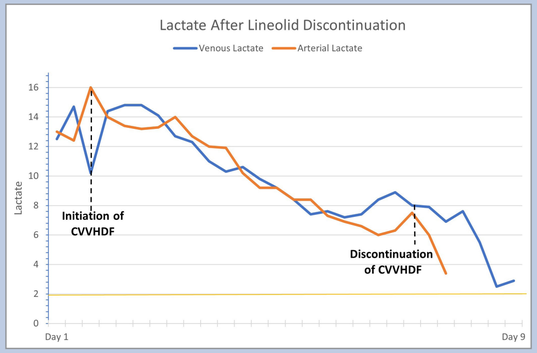

Figure 3. Comparison of venous and arterial lactate levels after linezolid discontinuation. Lactate level persisted to be elevated despite discontinuation of CVVHDF.

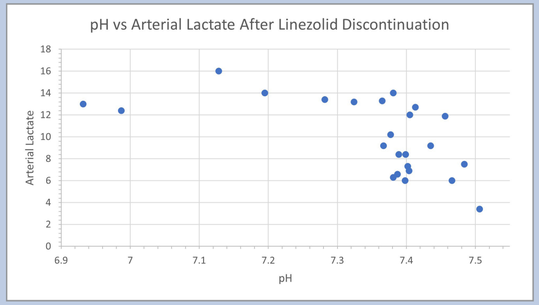

Figure 4. pH and arterial lactate levels after linezolid discontinuation. With aggressive bicarbonate resuscitation, using CRRT, we were able to maintain improved pH levels despite persistently elevated lactate levels.

Admission Day	Linezolid Day	Corrected Anion Gap	Na	Cl	HCO3
Day 1	21	16.2	132	108	12
Day 2	22	11.1	133	114	12
Day 3	23	12.6	138	116	14
Day 4	24	12.7	137	109	20
Day 5	25	14.7	137	104	23
Day 6	26	12.9	137	106	23
Day 7	27	14.3	132	103	20
Day 8	28	13.7	134	103	22
Day 9	29	13.7	134	103	22
Day 10	30	15.7	132	102	19
Day 11	31	13.7	133	103	21
Day 12 - POD 1	32	23.7	133	106	8
Day 12 - Start CVVHDF		26.7	139	110	7
Day 12		24.7	137	107	10
Day 13		21.7	138	103	18
Day 13		20.7	138	102	20
Day 13		22.7	140	104	18
Day 13		15.7	139	105	23
Day 13		15.7	138	107	20
Day 13		16.7	140	108	20
Day 14		13.7	139	108	22
Day 14		14.7	138	109	19
Day 14		14.7	140	109	21
Day 14		14.7	138	109	19
Day 14		12.7	137	108	21
Day 15		13.7	138	108	21
Day 15		14.7	138	108	20
Day 15		15.7	138	108	19
Day 16		15.7	139	107	21
Day 16		16.7	138	107	19
Day 16		13.7	137	107	21
Day 16		16.7	138	108	18
Day 17		13.4	137	108	19
Day 17 - DC CVVHDF		12.4	137	108	20
Day 18		14.6	138	104	23
Day 18		13.6	138	101	27
Day 19		10.9	136	102	27
Day 20		11.1	140	104	29
Day 21		6.3	138	106	30

Table 1. Anion gap corrected for hypoalbuminemia and electrolytes throughout admission. On presentation, she had a drop in bicarbonate with a mild gap, with improvement in HCO3 through fluid resuscitation. However, the corrected AG remained abnormally elevated until postoperatively, her HCO3 dropped and corrected AG elevated considerably.
Note: Day 4-11, AGMA persisted despite serum bicarbonate levels averaging 21.

Discussion

Prolonged linezolid use created a metabolic acidosis pre-operatively which predisposed to a severe drop in lactic acidosis post operatively.

- The risk of linezolid-associated lactic acidosis has been suggested to increase at 28 days of use[7], however, her lactic acidosis presented at day 21, and was so subtle that the patient was normotensive, and asymptomatic, and thus linezolid was continued.
- Immediately post-op for abscess drainage and ostomy revision, corrected AG jumped up to 27 and bicarbonate dropped to 8 mmol/L.

CRRT temporized the acidosis to provide enough NaHCO3 to keep pH > 7.2

- Linezolid is not efficiently removed by CRRT. Non-renal clearance accounts for 65% of linezolid excretion and its half life is around 5 hours.[8]
- Elimination of Linezolid through hemodialysis is around 40% and linezolid concentrations can be sustained in the blood despite undergoing dialysis.[9] Thus, CRRT use for this patient mainly provided aggressive bicarbonate supplementation to increase the pH > 7.25, with some clearance through dialysis.
- We initially provided a unique CRRT where high volume sodium bicarbonate at 75 meq/hour x 4 hours and thereafter 48 meq/hour was delivered. The acidosis persisted for several days despite CRRT - the CRRT was used for 5 continuous days.

Lactic acidosis of linezolid persisted for days despite discontinuation.

- Serum lactate levels remained elevated for 9 days.
- Knowledge of AGMA as a potential side effect of linezolid should help guide its use. The mitochondrial dysfunction known to occur may develop prior to 28 days of use (a dateline cited in the literature as when lactic acidosis risk increases[7]) and may not be clinically apparent at first, only rapidly being demonstrated when a patient experiences physiological stress.

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