

The risk factors of linezolid-induced lactic acidosis

A case report and review

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Abstract

Background: In recent years, linezolid is increasingly used in multidrug-resistant bacteria therapy. At the same time, linezolidinduced lactic acidosis has been continually reported as a serious side effect. Notably, to our knowledge, there are limited available literatures that evaluate risk factors for linezolid-induced lactic acidosis, and there is no highly reliable study on the relationship between linezolid-induced lactic acidosis and age or gender. However, clinicians need relevant information to advice on the use of linezolid. Therefore, we report on a case of life-threatening lactic acidosis after 3 doses of linezolid exposure and evaluate the risk factors of linezolid-induced lactic acidosis.

Methods: Cases of linezolid-induced lactic acidosis reported in PubMed were searched. Several characteristics and data of case numbers and deaths were extracted for analysis.

Results: A total of 35 articles including 47 cases were included in this study. Twelve patients (25.5%) died due to linezolid-induced lactic acidosis. At the cut-offs of 7, 14, and 28 days, the mortalities were 27.3%, 20%, and 27.3%. No statistically significant difference was observed according to age and gender. However, the proportion (27.7% and 29.8%) and mortality (30.8% and 35.7%) of male patients were much higher than females in both \geq 65 and <65 years old groups (proportion: 15.2% and 23.9%; mortality: 14.3% and 18.2%).

Conclusion: The mortality of linezolid-induced lactic acidosis was relatively high. The duration of linezolid use and age might not be risk factors. Gender (specifically, male) might be related to the mortality of linezolid-induced lactic acidosis.

Abbreviations: BPH = benign prostate hyperplasia, CDG-1A = congenital disorder of glycosylation type 1a, CKD = chronic kidney disease, CRRT = continuous renal replacement therapy, ESRD = end-stage renal disease, F = female, M = male, MAIC = *Mycobacterium avium*-intracellular complex, MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, MRSA = methicillin-resistant *Staphylococcus aureus*, NR = not reported, PM = polymyositis, SBE = subacute bacterial endocarditis, SCD = sickle cell disease, SLED = sustained low efficiency dialysis, VRE = vancomycin-resistant *Enterococcus faecium*.

Keywords: lactic acidosis, linezolid, mortality, proportion, risk factor

1. Introduction

Linezolid, an oxazolidinone antimicrobial, was approved for clinical use by the US Food and Drug Administration in 2000. Linezolid is useful against multidrug-resistant gram-positive bacteria, including vancomycin-resistant *Enterococcus faecium*, vancomycin-resistant *Staphylococcus aureus*, and methicillin-resistant *S aureus*. Its mechanism of action is inhibiting bacterial protein synthesis by binding to 23S ribosomal RNA in the 50S subunit, preventing fusion with the 30S subunit and formation of the initiation complex.^[1]

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Linezolid-induced lactic acidosis has already been reported,^[2] especially after prolonged use (≥28 days). It is a serious adverse drug reaction that can result in multiorgan failure and death. We noticed that various linezolid treatments (range from 1 day^[3] to 109 days)^[4] can cause lactic acidosis. The incidence is relatively low but always life-threatening. Therefore, clinicians require relevant information, such as the risk factors and data from similar cases, to advice on the clinical use of linezolid. Many studies have been done, and the most frequently referenced one is research from Korea,^[5] which had collected and analyzed reported cases of linezolid-induced lactic acidosis. They concluded that a long period of use is not a prerequisite for death.^[5] However, there were several limitations related to that research. First, the number of cases included was relatively small. Thirteen cases, 2 missed and 11 newly reported, were not included in that research. In addition, 2 duplicate cases presented in different literatures were not excluded.^[6,7] Second, the data extraction was not precise and accurate enough. For example, "90 days"^[6] in the original literature was replaced by "12 weeks." Moreover, several mistakes were found in converting from mg/dL to mmol/ L, which resulted in incorrect concentrations of lactate. "59 mg/ dL^{"[6]} should be converted to "6.5 mmol/L" instead of "5.9 mmol/L," and "113.4 mg/dL"^[8] was equal to "12.6 mmol/L" instead of "12.1 mmol/L," etc. These limitations would result in inaccurate and, very likely, falsely negative conclusions. In addition, to our knowledge, there is no highly reliable study on

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the relationship between linezolid-induced lactic acidosis and age or gender.

Therefore, we searched for reported cases of linezolid-induced lactic acidosis and extracted the data accurately to evaluate the risk factors. In addition, we also report a life-threatening case of lactic acidosis after 3 doses of linezolid exposure.

2. Case report

A 57-year-old man was admitted to the Pneumology Department of the Affiliated Hospital of Medical School, Ningbo University in December 2016 for cough and sputum production for half a month and hemoptysis for 1 day. He had a medical history of pulmonary aspergillosis and type 2 diabetes.

On admission, blood pressure was 125/76 mm Hg, the body temperature was 36.6°C, respiratory rate was 19 breaths/min, and heart rate was 79 beats/min. Results of laboratory tests included the following values: urea nitrogen 12.4 mmol/L, creatinine 139.7 μ mol/L, uric acid 539 μ mol/L, potassium 4.43 mmol/L, glucose 7.83 mmol/L, leukocytes 12 \times 10⁹/L, with 75.6% neutrophils, hemoglobin 11.4 g/dL, lactic acid 1.9 mmol/L, and pH 7.37.

Intravenous voriconazole (200 mg q/12 h, first dose doubling) was used to treat pulmonary fungal infection. The results of a sputum smear examination showed gram-positive cocci+, gram-positive bacilli+, and gram-negative bacilli+. According to the results of sputum smear examination and the clinical manifes-tations, community-acquired pneumonia cannot be excluded and moxifloxacin (400 mg q/d) was added on day 3. Five days later, the patient presented with shortness of breath and became febrile up to 38.8°C. Chest radiography showed aggravated infection. Intravenous imipenem and cilastatin sodium (500 mg q/8 h) was substituted for moxifloxacin.

The patient was transferred to the intensive care unit on day 10 for severe pneumonia-induced respiratory failure. The antibiotic therapy was escalated to vancomycin. Because of poor renal function (estimated renal clearance 36 mL/min), intravenous linezolid (600 mg q/12 h) was introduced as an alternative treatment to vancomycin. After 3 doses of linezolid, the patient's blood lactate had risen up to 10.0 mmol/L, blood pressure was 50/40 mm Hg, heart rate was 42 beats/min, and creatinine was $335.8 \,\mu\text{mol/L}$. Noradrenaline and dopamine were administered with a minipump to maintain a relatively normal pressure. As linezolid was implicated as a possible cause of the lactic acidosis, the agent was discontinued.

The patient required mechanical ventilation because of respiratory failure and continuous renal replacement therapy for 6 days to normalize his blood pH and clear linezolid from his plasma. However, the lactic acidosis improved only marginally, and his blood pressure decreased to 30/22 mm Hg. The patient died on day 17.

2.1. Data sources

We searched for cases of linezolid-induced lactic acidosis reported in English in PubMed from their inception until April 2017. Literature searches included keywords for "linezolid" or "Zyvox" and "lactic acidosis" or "hyper-lactatemia."

2.2. Case selection

Two reviewers (Yiyang Mao and Danping Dai) independently screened all titles and abstracts for eligible articles. Cases

presented in the articles were included if the lactic acidosis was induced by linezolid and the data were extractable.

2.3. Data extraction

Two authors extracted data independently (Yiyang Mao and Danping Dai). Any dispute was settled by discussion or by a third investigator. Study characteristics were extracted from each case, including first author identification, gender, age, comorbidities, reason for use, duration of linezolid, dosage, lactate concentration before linezolid, peak lactate concentration after linezolid, treatment for lactic acidosis, and outcome.

Seven, fourteen, and twenty-eight days were selected to be the cut-off points in statistics according to the treatment duration recommended in the drug instruction. The treatment duration of linezolid was expressed in days in the calculations. The dosage of linezolid was assumed to be 600 mg/bid, when it was not reported according to the drug instruction. Only the lactic acidosis-related deaths were included when analyzing and evaluating the data. Patients ≥ 65 years were defined as elderly according to the WHO's definition.

2.4. Data analysis

All statistical analyses were conducted using the SPSS software package (version 18.0). Statistical evaluations were carried out using the chi-squared tests with *P* values of <.05 considered to be statistically significant. All statistical tests were 2-sided. Fisher exact test was used when the sample size was <40.

3. Results

The case selection process for inclusion is shown in Fig. 1. The electronic searches identified 54 potentially relevant articles. After initially screening, 40 relevant articles were selected, and



Gut off (in)	Case	Gender	Age, y	Comorbidities	Disease for use	Duration	Dosage	Lactate before, mmol/L	Peak lactate, mmol/L	Treatment	Outcome
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Table 1

BPH = benign prostate hyperpasis, CDG-1A = companital disorder of glycosylation type 1a, CKD = chronic kidney disease, CRRT = continuous renal replacement therapy, ESRD = end-stage renal disease, F = female, M = male, MAIC = *Mycobacterium avium*-intracellular complex, MELAS = mithochondrial encephalomypoathy, lactic acidosis, and stroke-like episodes, MRSA = methicillin-resistant *Staphylococcus aureus*, INE = not reported, PM = polymyositis, SBE = subacute bacterial endocarditis, SCD = sickle cell disease, SLED = sustained low efficiency dialysis, VRE = vancomycin-resistant *Entercoccus faecium*.

Table 2	2		
Summary	of different duration	n of linezolid therapy.	
	Day 7	Day 14	Day 28
n	11	15	22
m	3	3	6

m = the number of lactic acidosis-related deaths, n = the number of linezolid-induced lactic acidosis.

5 reviews and 2 duplicate cases were excluded. A total of 35 articles including 47 cases were included.

The characteristics of the included cases are shown in Table 1. The mean duration of linezolid use was 64.1 days. Twelve patients (25.5%) died due to linezolid-induced lactic acidosis. Of the 47 cases, 28 were males and 18 were females. One patient's gender and one male patient's age were not reported.

The summary of different durations of linezolid therapy is shown in Table 2. At the cut-offs of 7, 14, and 28 days, the mortalities were 27.3%, 20%, and 27.3%, respectively. Because the sample size was too small, statistical analysis was not possible.

The statistics of different sex and ages are shown in Table 3. The 2 cases in which the information of patient gender or age was missing were not counted. In the male group, the proportions of patients ≥ 65 and <65 years were 27.7% and 29.8%, and the mortalities were 30.8% and 35.7%, respectively. In the female group, the proportions of patients ≥ 65 and <65 years were 15.2% and 23.9%, and the mortalities were 14.3% and 18.2%, respectively. Fisher exact tests were used because the sample sizes were <40. The difference in mortality between the 2 gender groups was not significant for either the ≥ 65 or <65 years group (P=.613; P=.407). The difference in mortality between the 2 age groups was not significant for either the male or female group (P=1.000; P=1.000).

4. Discussion

The mortality of linezolid-induced lactic acidosis (25.5%) in our study was similar to Im et al's data.^[5] This may be because the onset of lactic acidosis was usually abrupt and the majority of patients developed serious respiratory failure. However, as we known, metformin can cause lactic acidosis too. A research including 253 cases showed that the mortality of metformin-associated lactic acidosis was 17.2%.^[9] The mortality of linezolid-induced lactic acidosis was considered to be relatively high.

Our study found that the mortality did not increase as the duration of linezolid therapy increased. Therefore, we considered that the duration might not be a risk factor. However, mortalities at every cut-off day were extremely high. Therefore, we should pay attention to the patients' vital signs, no matter when the patients suffered the linezolid-induced lactic acidosis.

The mortalities did not correlate with gender and age according to our statistical results. However, the proportions

Table 3 Statistics of different sex and ages.					
	Male, n (m)	Female, n (m)	<i>P</i> value for death [*]		
≥65 years old <65 years old <i>P</i> value for death [*]	13 (4) 14 (5) 1.000	7 (1) 11 (2) 1.000	.613 .407		

Two cases in which the information of patient gender or age was missing were not counted. m = the number of lactic acidosis-related deaths, n = the number of linezolid-induced lactic acidosis. * P values were carried out by Fisher exact tests. of male patients were significantly higher than female patients in both age groups. Male patients seemed to be more susceptible to linezolid-induced lactic acidosis. Notably, male patients had twice the mortalities compared with female patients in both age groups.

Because the action mechanism of linezolid is related closely to the mitochondrion, we suspected that a gene might play a key role and that the linezolid-induced acid acidosis might be genetic. We thought that this may explain why the duration of linezolid was not a risk factor when gender might be related to lactic acidosis. As early as 2004, a research report from Taiwan indicated that there was a very strong association between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome.^[10] If there exists a specific gene that is related to linezolid-induced lactic acidosis, screening for that gene can be performed prior to initiation of linezolid treatment to prevent the occurrence of linezolid-induced lactic acidosis. However, as far as we know, limited genetic association studies have been performed. For example, Palenzuela et al^[22] investigated potential for contribution from mitochondrial polymorphisms. Therefore, further studies between different races, families, and alleles seem to be needed.

This study has a number of limitations. First is the relatively small sample size. Therefore, more relevant cases need to be reported to support further evaluation, and more studies with larger numbers are needed to certify our results. Second, as this was a case review study, we cannot exclude confounding factors such as disease severity. Thus, some bias may exist in this study.

In conclusion, the mortality of linezolid-induced lactic acidosis was considered to be relatively high. Duration of linezolid therapy might not be a risk factor for death related to linezolidinduced lactic acidosis. The mortalities did not correlate with gender and age according to the statistical results. However, male patients had high mortality from linezolid-induced lactic acidosis. Linezolid's potential-associated lactic acidosis requires systematic monitoring during clinical therapy. The genetic factor could be considered in future studies.

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Author contributions

Haiying Jin conceived and designed the study, provided general advice, and revised the manuscript. Yiyang Mao performed the searches, extracted the data, performed the data analysis, and wrote the manuscript. Danping Dai performed the searches and extracted the data. Yangyang Wang conducted the searches and provided a clinical perspective. All authors have read and approved the final version of the manuscript.

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