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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, linezolid-induced 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 ≥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]

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 μmol/L, uric acid 539 μmol/L, potassium 4.43 mmol/L, glucose 7.83 mmol/L, leukocytes 12 $\times$ 10^9/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 manifestations, 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 μmol/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

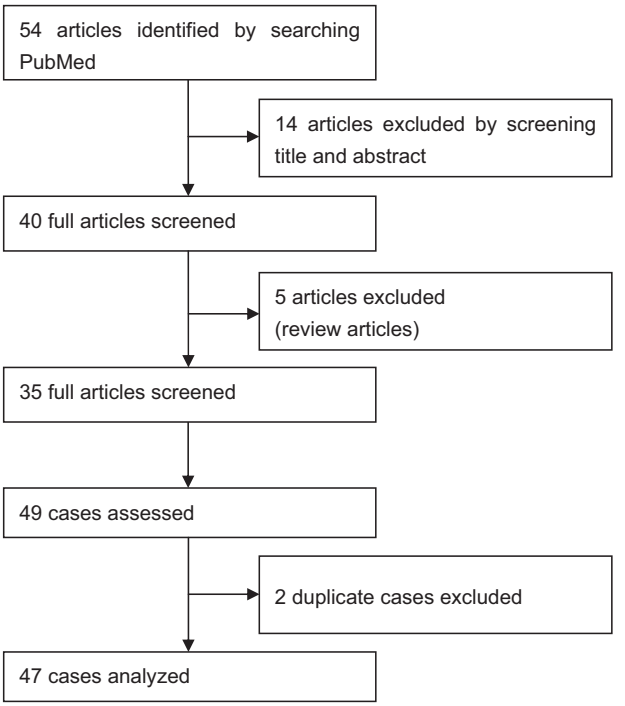

Figure 1. Flow chart of the case selection.

Table 1

Demographic, clinical, and laboratory characteristics of reported cases of linezolid-induced lactic acidosis.

Case	Gender	Age, y	Comorbidities	Disease for use	Duration	Dosage	Lactate before, mmol/L	Peak lactate, mmol/L	Treatment	Outcome
Su et al[11]	M	6 mo	Liver transplantation	VRE sepsis, pneumonia	32 d	NR	pH 7.37	24	CRRT	Died
	F	6 mo	CDG-1A	Pneumonia	31 d	NR	0.9–1.6	38.1	Cardiovascular support	Died
	M	16	Cryptogenic cirrhosis	Urinary tract infection	7 d	NR	0.9	28	CRRT	Died
Im et al[5]	M	64	Diabetes	Soft tissue infection	7 wk	NR	NR	20 (pH 6.91)	Hemodialysis	Died
	M	77	Diabetes	Prosthetic infection	4 wk	NR	NR	16 (pH 7.1)	Hemodialysis	Died
	F	53	Cancer	Urinary tract infection	1 wk	NR	NR	(pH 7.19)	Bivone	Survived
	M	76	Diabetes	Soft tissue infection	1 wk	NR	NR	4.5	Discontinued	Survived
	F	69	Diabetes	Prosthetic infection	5 wk	NR	NR	4.8	Discontinued	Survived
Del Pozo et al[12]	F	72	Liver transplantation	Nocardiosis	13 wk	600 mg bid	NR	4.8	Thiamine	Survived
	M	43	Liver transplantation	Tuberculosis	8 wk	600 mg bid	NR	7.2	Thiamine	Survived
Cope et al[13]	M	20	MELAS	Pneumonia	2 d	600 mg bid	3.4	7	Hemodialysis	Survived
Johnson et al[14]	M	34	SCD, ESRD	Polymicrobial line infection	11 d	600 mg bid	2.1	26	Discontinued	Survived
Zuccarini et al[15]	F	67	Hip replacement	Ost-operative MRSA infection	6 wk	NR	NR	9.4	Discontinued	Survived
Abou Hassan et al[16]	M	74	Knee prosthesis implantation	Prosthesis infection	21 d	600 mg bid	NR	21 (pH 6.9)	Hemodialysis, bicarbonate	Survived
Apodaca and Rakita[2]	F	52	NR	Pneumonia	13 wk	NR	NR	>9.9	Discontinued	Survived
Bernard et al[17]	M	81	Serotonin syndrome	Osteomyelitis	3 wk	600 mg bid	NR	29.1 (pH 6.9)	Discontinued	Died
Boutoille et al[4]	M	48	NR	Multidrug-resistant tuberculosis	109 d	600 mg bid	NR	11.6	Discontinued	Died
Cabajo et al[18]	M	79	BPH, CKD stage 4	Prosthetic infection	7 wk	NR	NR	3.11 (pH 7.25)	Discontinued	Survived
Carson et al[19]	F	35	AIDS	Disseminated infection with MAIC	35 d	600 mg bid	NR	20.5 (pH 7.16)	Thiamine, hemodialysis	Survived
Contou et al[3]	M	81	Hepatitis-C-associated cryoglobulinemia	Pneumonia	1 d	600 mg bid	2 (pH 7.47)	16 (pH 7.03)	Thiamine	Died
Djibré et al[20]	M	70	Alcoholic liver cirrhosis	Pneumonia	15 d	NR	NR	23 (pH 6.89)	CRRT	Died
Hsu et al[21]	F	38	Alcoholic cirrhosis, child B and CKD stage 3	VRE urinary tract infection	12 d	NR	NR	24 (pH 6.918)	Thiamine	Survived
Palenzuela et al[22]	F	74	Chronic anemia	Prosthetic infection	47 d	NR	NR	18.4	Discontinued	Died
	F	49	Bone marrow transplantation	VRE sepsis	58 d	NR	NR	13.3	Discontinued	Survived (died 1 mo later for other reason)
Protti et al[23]	M	64	Lung transplantation	Pneumonia	4 d	600 mg bid	NR	>20	Hemodialysis	Died
Sawyer et al[24]	M	63	PM	Chest wall abscess secondary to pulmonary nocardiosis	85 d	600 mg bid	NR	23.199	SLED, sodium bicarbonate	Survived
Scotton et al[25]	F	81	NR	Tuberculous spondylodiscitis	12 d	600 mg bid	NR	18.6 (pH 7.24)	Discontinued	Survived
Velez and Janech[26]	M	36	ESRD	Pneumonia	6 wk	600 mg bid	NR	13.2	Hemodialysis	Survived
Wiener et al[27]	F	80	Mitral valve replacement	VRE bacteremia	19 d	NR	2.1	19 (pH 7.026)	Thiamine	Survived
Miyawaki et al[28]	M	75	Gastric cancer	Pyogenic spondylitis	72 d	600 mg bid	(pH 7.495)	>25	Hemodialysis	Survived
Lee et al[29]	F	56	Renal transplantation	Urinary tract infection	4 d	600 mg bid	NR	4.3	Discontinued	Survived
Bishop et al[30]	M	NR	NR	NR	24 d	600 mg bid	NR	10	NR	Survived
De Bus et al[8]	F	55	Rheumatoid arthritis	Malnutrition and chronic infection	50 d	600 mg bid	0.9	12.6	Hemodialysis	Died
Garrabou et al[6]	F	74	Sd. Sjögren	Hip prosthetic infection	44 d	600 mg bid	NR	3	NR	Survived
	M	83	NR	Knee prosthetic infection	30 d	600 mg bid	NR	4.8	Discontinued	Survived
	M	25	Knee osteosarcoma	Knee prosthetic infection	90 d	600 mg bid	NR	6.5	Discontinued	Survived
	M	75	Waldenström macroglobulinemia	Central nervous system infection	80 d	600 mg bid	NR	3.1	Discontinued	Survived
	M	65	Diabetes mellitus	Knee prosthetic infection	35 d	600 mg bid	NR	4.9	Discontinued	Survived
Soriano et al[7]	NR	5	NR	Prosthetic infection	6 wk	NR	NR	4.4	Discontinued	Survived
Pea et al[31]	M	59	Liver transplantation	Pneumonia	1 wk	600 mg bid	NR	8.4	Discontinued	Survived
Vu and Walia[32]	M	36	Metastatic cancer	Soft tissue infection	1 wk	600 mg bid	NR	13.5	Discontinued	Survived (died later for other reason)
De Vriese et al[33]	F	63	NR	Prosthetic infection	16 d	NR	NR	24.5	Discontinued	Survived (blind)
Thorell et al[34]	F	13	Sickle cell anemia	Mediastinum abscess	9 wk	600 mg bid	NR	NR	Discontinued	Survived
Lee et al[35]	F	56	Kidney transplantation	Urinary tract infection	1 d	NR	NR	4.7	Discontinued	NR
Fernández de Orueta et al[36]	M	72	SBE	NR	5 wk	NR	NR	13.8	Discontinued	NR
Kopterides* et al[37]	M	70	Lymphoma	Pneumonia	1 wk	NR	NR	12.5	Thiamine	Survived
Kraleti and Soultanova[38]	M	32	Nonischemic cardiomyopathy	Empyema	14 d	NR	NR	4.5	Discontinued	Survived

* Data of this case is extracted from Im et al's study.[5]

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*.

Table 2

Summary of different duration 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 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.

Table 3

Statistics of different sex and ages.

	Male, n (m)	Female, n (m)	*P* value for death*
≥65 years old	13 (4)	7 (1)	.613
<65 years old	14 (5)	11 (2)	.407
P value for death*	1.000	1.000	

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.

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 linezolid-induced 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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Formal analysis: Yiyang Mao, Haiying Jin.
Writing – original draft: Yiyang Mao.
Writing – review & editing: Yiyang Mao, Haiying Jin, Danping Dai, Yangyang Wang.

References

[1] Colca JR, McDonald WG, Waldon DJ. Cross-linking in the living cell locates the site of action of oxazolidinone antibiotics. J Biol Chem 2003;278:21972–9.

[2] Apodaca AA, Rakita RM. Linezolid-induced lactic acidosis. N Engl J Med 2003;348:86–7.
[3] Contou D, Focjet J, Grimaldi D, Cariou A. Early life-threatening lactic acidosis following a single infusion of linezolid. Int J Antimicrob Agents 2011;38:84–5.
[4] Boutoille D, Grossi O, Depatureaux A, Tattevin P. Fatal lactic acidosis after prolonged linezolid exposure for treatment of multidrug-resistant tuberculosis. Eur J Intern Med 2009;20:e134–5.
[5] Im JH, Baek JH, Kwon HY, Lee JS. Incidence and risk factors of linezolid-induced lactic acidosis. Int J Infect Dis 2015;31:47–52.
[6] Garrabou G, Soriano A, Lopez S, et al. Reversible inhibition of mitochondrial protein synthesis during linezolid-related hyperlactatemia. Antimicrob Agents Chemother 2007;51:962–7.
[7] Soriano A, Miro O, Mensa J. Mitochondrial toxicity associate with linezolid. N Engl J Med 2005;353:2305–6.
[8] De Bus L, Depuydt P, Libbrecht L, et al. Severe drug-induced liver injury associated with prolonged use of linezolid. J Med Toxicol 2010;6:322–6.
[9] Yeh HC, Ting IW, Tsai CW, et al. Serum lactate level and mortality in metformin-associated lactic acidosis requiring renal replacement therapy: a systematic review of case reports and case series. BMC Nephrol 2017;18:229.
[10] Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens–Johnson syndrome. Nature 2004;428:486.
[11] Sue E, Crowley K, Carcillo JA, Michaels MG. Linezolid and lactic acidosis: a role for lactate monitoring with long-term linezolid use in children. Pediatr Infect Dis J 2011;30:804–6.
[12] Del Pozo JL, Fernandez-Ros N, Saez E, et al. Linezolid-induced lactic acidosis in two liver transplant patients with the mitochondrial DNA A2706G polymorphism. Antimicrob Agents Chemother 2014;58:4227–9.
[13] Cope TE, McFarland R, Schaefer A. Rapid-onset, linezolid-induced lactic acidosis in MELAS. Mitochondrion 2011;11:992–3.
[14] Johnson PC, Vaduganathan M, Philips KM, O'Donnell WJ. A triad of linezolid toxicity: hypoglycemia, lactic acidosis, and acute pancreatitis. Proc (Bayl Univ Med Cent) 2015;28:466–8.
[15] Zuccarini NS, Yousuf T, Wozniczka D, Rauf AA. Lactic acidosis induced by linezolid mimics symptoms of an acute intracranial bleed: a case report and literature review. J Clin Med Res 2016;8:753–6.
[16] Abou Hassan OK, Karnib M, El-Khoury R, et al. Linezolid toxicity and mitochondrial susceptibility: a novel neurological complication in a Lebanese patient. Front Pharmacol 2016;7:325.
[17] Bernard L, Stern R, Lew D, Hoffmeyer P. Serotonin syndrome after concomitant treatment with linezolid and citalopram. Clin Infect Dis 2003;36:1197.
[18] Carbajo T. Lactic acidosis and linezolid-induced pancytopaenia. Nefrologia 2011;31:107–8.
[19] Carson J, Cerda J, Chae JH, et al. Severe lactic acidosis associated with linezolid use in a patient with the mitochondrial DNA A2706G polymorphism. Pharmacotherapy 2007;27:771–4.
[20] Djibré M, Pham T, Denis M, et al. Fatal lactic acidosis associated with linezolid therapy. Infection 2015;43:125–6.
[21] Hsu SN, Shih MF, Yang CW, et al. Severe linezolid-induced lactic acidosis in a cirrhosis patient. Nephrology (Carlton) 2015;20:47–8.
[22] Palenzuela L, Hahn NM, Nelson RPJr, et al. Does linezolid cause lactic acidosis by inhibiting mitochondrial protein synthesis? Clin Infect Dis 2005;40:e113–6.
[23] Protti A, Ronchi D, Bassi G, et al. Changes in whole-body oxygen consumption and skeletal muscle mitochondria during linezolid-induced lactic acidosis. Crit Care Med 2016;44:e579–82.
[24] Sawyer AJ, Haley HL, Baty SR, et al. Linezolid-induced lactic acidosis corrected with sustained low-efficiency dialysis: a case report. Am J Kidney Dis 2014;64:457–9.
[25] Scotton P, Fuser R, Torresan S, et al. Early linezolid-associated lactic acidosis in a patient treated for tuberculous spondylodiscitis. Infection 2008;36:387–8.
[26] Velez JC, Janech MG. A case of lactic acidosis induced by linezolid. Nat Rev Nephrol 2010;6:236–42.
[27] Wiener M, Guo Y, Patel G, Fries BC. Lactic acidosis after treatment with linezolid. Infection 2007;35:278–81.
[28] Miyawaki A, Ueda T, Nakao A, et al. Linezolid-induced lactic acidosis followed by severe hypophosphatemia after discontinuation of linezolid. Surg Infect (Larchmt) 2013;14:229–30.
[29] Lee YR, Powell N, Bonatti H, et al. Early development of lactic acidosis with short term linezolid treatment in a renal recipient. J Chemother 2008;20:766–7.
[30] Bishop E, Melvani S, Howden BP, et al. Good clinical outcomes but high rates of adverse reactions during linezolid therapy for serious infections: a proposed protocol for monitoring therapy in complex patients. Antimicrob Agents Chemother 2006;50:1599–602.
[31] Pea F, Scudeller L, Lugano M, et al. Hyperlactacidemia potentially due to linezolid overexposure in a liver transplant recipient. Clin Infect Dis 2006;42:434–5.
[32] Vu N, Walia R. Linezolid-induced lactic acidosis. Chest J 2006;130: 337S–8S.
[33] De Vriese AS, Coster RV, Smet J, et al. Linezolid-induced inhibition of mitochondrial protein synthesis. Clin Infect Dis 2006;42:1111–7.
[34] Thorell EA, Sharma M, Jackson MA, et al. Disseminated nontuberculous mycobacterial infections in sickle cell anemia patients. J Pediatr Hematol Oncol 2006;28:678–81.
[35] Lee HJ, Choi JH, Kim SY, et al. A case of linezolid-associated lactic acidosis. Korean J Med 2012;82:371–3.
[36] Fernández de Orueta N, Diaz V, Ramirez M, Alvarez R. Linezolid-induced lactic acidosis. Enferm Infecc Microbiol Clin 2009;27:550–1.
[37] Kopterides P, Papadomichelakis E, Armaganidis A. Linezolid use associated with lactic acidosis. Scand J Infect Dis 2005;37:153–4.
[38] Kraleti M, Soultanova I. Pancytopenia and lactic acidosis associated with linezolid use in a patient with empyema. J Ark Med Soc 2013;110:62–3.