A retrospective study of the risk factors for linezolid - induced haematological toxicity in Chinese patients

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Abstract

Purpose: To investigate the risk factors of linezolid-induced haematological toxicity in hospitalized patients.

Methods: In this retrospective, single-center, observational cohort study, patients underwent linezolid TDM trough concentration (Cmin) during treatment between January 2020 and December 2021 were analysed.Univariate and multivariate logistic regression analysis were used to investigate the relevant risk variables, and a relative operating characteristic (ROC) curve was generated to predict clinical characteristics.

Results: A total of 111 valid individuals were studied, among which 47 were diagnosed with linezolidine-related thrombocytopenia and 18 were diagnosed with linezolidine-related hemoglobin decrease, respectively. Binary logistic regression analysis showed that creatinine clearance level (Ccr) <50 ml/min/1.73 m^2 [OR, 5.463; 95% CI, 1.249-23.888, P=0.024] and the plasma trough concentration >7mg/L [OR, 62.660; 95% CI, 14.293-274.708, P=0.001] were risk factors associated with thrombocytopenia induced by linezolid. The area under the ROC curve of linezolid plasma trough concentration was 0.955, the Youden index was 0.837 at the maximum, and the corresponding critical value was 6.94 mg/L, with a sensitivity of 91.5% and a specificity of 92.2%. Moreover, Ccr <50 ml/min/1.73 m^2 [OR, 7.282; 95% CI, 1.765-30.048, P=0.006] and the plasma trough concentration >7mg/L[OR, 6.364; 95% CI, 1.937-20.910, P=0.020] were closely related to linezolid related hemoglobin reduction. The area under the ROC curve of linezolid plasma trough concentration was 0.755, the Youden index was 0.477 at the maximum, and the corresponding critical value was 7.53 mg/L, with a sensitivity of 77.8% and a specificity of 69.9%.

Conclusion: Renal insufficiency is a related risk factor for linezolid-induced haematological toxicity. It is recommended that patients treated with linezolid should monitor blood routine and plasma concentration, especially in patients with moderate or severe renal insufficiency. Plasma trough concentration of linezolid could be a suitable predictor for linezolid-related thrombocytopenia and anemia.

Introduction

Linezolid, the first antibiotic in the oxazolidinone family, is commonly employed against Gram-positive bacteria[1], such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Staphylococcus aureus* (VRSA), vancomycin-resistant *Enterococcus* (VRE), and others[2-5]. Hematologic side effects, including anemia, leukopenia and thrombocytopenia, have been reported during post-marketing clinical use of linezolid. Previous studies have revealed that risk factors of linezolid-induced haematological toxicity included renal damage, chronic liver disease, linezolid therapy duration (>14 days), and low baseline platelet count[6-12]. Moreover, the incidence of side effects was inconsistent with that recorded in the drug instruction. According to the prescribing information, there was no significant change in pharmacokinetic parameters in patients with or without mild and moderate hepatic and renal

insufficiency. Therefore, the dose of linezolid could be administrated normally. However, this is inconsistent with clinical trial[13]. Herein, we report on our investigation of possible risk factors to provide a reference for clinical drug safety and minimize the incidence of linezolid-induced haematological toxicity.

Patients And Methods

Patients

Data were collected on hospitalized patients who received linezolid anti-infection treatment in a class-A tertiary hospital in Guangxi between January 2020 and December 2021. Inclusion criteria were the following: the duration of linezolid therapy ≥4 days; the plasma trough concentration was monitored during linezolid treatment. The exclusion criteria were as follows: incomplete clinical medical records; patients with basic haematological diseases; age <18 years; radiotherapy and chemotherapy patients with malignant tumors; patients allergic to linezolid.

Data collection

Data collection was conducted based on the hospital information management records retrieval system. Using linezolid as an index, we finally included 111 patients for the study according to the inclusion and exclusion criteria from the medical and health electronic database of medication orders. The basic characteristics of patients were collected, including gender, age, body weight, combined antibiotics, route and type of administration, duration of linezolid treatment, plasma trough concentration and laboratory data (blood routine examination, total protein concentration, albumin concentration, liver function, kidney function and inflammatory parameters).

Determination of plasma trough concentration

Patients were treated with linezolid at a daily dose (600 mg, q12h) for more than 3 days. Blood samples were collected at 30 min before the next dose in steady-state conditions. A validated high-performance liquid chromatography (HPLC) method was carried out to determine the concentration of linezolid in plasma. The linear range of linezolid concentration was 0.35-50 mg/L. The lowest detectable concentration was 0.05 mg/L. The intraday and interday accuracy and precision were within 10%. This study was approved by the ethics committee of first People's hospital of Nanning.

Assessment of haematological toxicity

Definition of haematological toxicity were as follows: (1) Thrombocytopenia: a reduction of ≥25% of platelet count compared to the baseline level or platelet count ≤100×10^9/L; (2) Anemia: the hemoglobin value drops to 75% or less of the lower limit of normal (male <120g/L, female <110g/L), or decreases by more than 25% from the baseline value; (3) Leukopenia: white blood cell < 4×10^9/L. The baseline value was collected at the beginning of linezolid therapy. In the absence of patient data on the first day of

linezolid treatment, the clinical data before the administration of linezolid could be used as the baseline haematological parameters.

Statistical analysis

Data were analyzed using SPSS 23.0 software. For comparisons between two groups, enumeration data were expressed as percentages, and measurement data were expressed as mean ± standard deviation or as the median, respectively. Continuous variables with normally distributed were analyzed using the Student's t-test, while the non-normally distributed variables were compared via the Mann-Whitney U test. Besides, categorical variables were conducted on Pearson's χ test. Finally, binary logistic regression analysis was applied to determine the risk factors associated with linezolid-induced haematological toxicity. The *p* value <0.05 was considered statistically significant in the study. The receiver operating characteristic curve (ROC) was drawn based on relevant continuous variables in the multivariate analysis to predict clinical features.

Results

Characteristics of patients

According to the inclusion and exclusion criteria, 111 patients were evaluated in this study. The ratio of male to female was 76 to 35, the median age was 64.0 years, and the median weight was 60.0 kg. Meanwhile, the median duration of linezolid treatment was 10.0 days. In this study, patients were administrated linezolid 600 mg q12h intravenously. The average linezolid concentration was 5.84 mg/L during the first therapeutic drug monitoring. After the treatment of linezolid, thrombocytopenia occurred in 47 patients (42.34%), and anemia in 18 patients (16.22%), respectively. No patients with leukopenia were observed in the study. The clinical characteristics of the patients are shown in Table 1.

Assessment of thrombocytopenia

47 of 114 patients were assessed for linezolid-related thrombocytopenia. Significant differences in age (P <0.0001), alanine aminotransferase(ALT, P=0.010), urea nitrogen (BUN, P <0.0001), serum creatinine (SCr, P<0.0001), creatinine clearance (Ccr, P <0.0001) and plasma trough concentration (P <0.0001) were found between patients with and without thrombocytopenia (Table 2).

The relationship between renal function and the plasma trough concentration of linezolid was further explored, with results indicating that the level of linezolid in patients with moderate and severe renal dysfunction was significantly higher than that in patients with normal renal function. The results were shown in Table 3.

As shown in Figure 1, the ROC curve was drawn based on the plasma trough concentration of linezolid. The area under the curve was 0.955, the maximum Youden index was 0.837, corresponding to the critical value of 6.94mg/L, the sensitivity was 91.5%, and the specificity was 92.2%, respectively.

A multivariate logistic regression analysis to identify risk factors for the development of thrombocytopenia extracted the following variables: age, ALT, AST, basal hemoglobin, glomerular filtration rate, and plasma trough concentration. We identified 2 independent risk factors for thrombocytopenia in patients with linezolid therapy: Ccr <50 mL/min/1.73 m^2 [OR, 5.463，95% CI, 1.249-23.888, P=0.024]，the plasma trough concentration >7mg/L[OR, 62.660, 95% CI, 14.293-274.708, P=0.001]. The results were shown in Table 4.

Assessment of anemia

Out of 114 patients, anemia occurred in 18 who received linezolid injection. Table 5 show that AST、total bilirubin、BUN、SCr、Ccr and plasma trough concentration were Significant variables.

The area under the ROC curve of linezolid plasma trough concentration was 0.755, the Youden index was 0.477 at the maximum, and the corresponding critical value was 7.53 mg/L, with a sensitivity of 77.8% and a specificity of 69.9% (Figure 2).

Binary logistic regression analysis indicated a signifcant correlation between linezolid-induced anemia and CCr <50 ml/min/1.73 m^2 [OR, 7.282, 95% CI, 1.765-30.048, P=0.006], and plasma trough concentration of linezolid >7μg/mL [OR, 6.364; 95% CI, 1.937-20.910, P=0.020] after eliminating the confounding factors (Table 6).

Discussion

Although the mechanism of haematological toxicity during linezolid medication is not clear, previous studies point to a correlation with reversible bone marrow suppression[14,15] and immune mediation[16]. In this study, the rate of linezolid-induced thrombocytopenia was 42.34% and anemia was 16.22%, respectively. We speculated that the differences between the findings of our study and prescribing information were related to the following limitations: the standard of adverse reactions to blood system damage has not been unified; research program and severity of research object; the combination of linezolid therapy, multi-dose administration design.

According to the medicine label sheet and multiple studies, pharmacokinetic characteristics in individuals with impaired renal function can rarely change, the dose of linezolid can be administrated as patients with normal renal function[13,17]. However, poor renal function was identified as an independent risk factor leading haematological toxicity during linezolid therapy, as validated in early reports[9,10,18-21]. In our study, a standard dose was given to each patient, the results showed that the patients with Ccr <50 mL/min were higher in the incidence of linezolid-induced thrombocytopenia and anemia, and higher plasma trough concentration than those with normal creatinine clearance at the start of the treatment. A large number of studies have stated that the risk of linezolid-related haematological toxicity was associated with a lower clearance rate of linezolid in renal insufficiency patients and an overexposure dose[9,17,19]. In addition, the accumulation of the major metabolites of linezolid has previously been

observed in individuals with renal dysfunction as possibly associated with this toxicity[22]. Therefore, we recommended that the dose adjustment of linezolid should be described in the drug label sheet to ensure the safety of patients with renal insufficiency.

In fact, the therapeutic window of linezolid was 2-7 μg/mL[17,23,24]. Concerning other identified risk factors, we found that trough level >7μg/mL was also considered a significant risk for haematological toxicity in hospitalized adults. In our study, the patients with haematological toxicity have a high trough level than those without haematological toxicity. The ROC curve indicated that the critical values of trough concentration for thrombocytopenia and anemia were 6.94μg/mL and 7.53μg/mL, respectively. For every 1 unit increase in trough concentration, the incidence of thrombocytopenia and anemia increased 62.6and 6.3 times, respectively. Therefore, we suggested that inpatients (especially patients with moderate and severe renal insufficiency) should be monitored for therapeutic drugs after the steady-state treatment with linezolid. Meanwhile, a blood routine examination should be performed during the stages of linezolid therapy. Notably, it could be anticipated that among patients the role of proactive therapeutic drug monitoring in personalizing linezolid therapy may be especially helpful.

The indicators of hepatic function (such as total bilirubin, ALT and AST) were not associated with the risk of thrombocytopenia, differently from what was observed in several previous studies[17,25-27]. This apparent discrepancy may be explained by the fact that just a few patients were included with liver insufficiency and the change of this indicator was not significant in some patients with liver function impairment. The lack of a control arm and the limited sample size may restrict the generalizability of the findings. Further study still needs to be performed to explain the relationship between the indicators and anemia. Therefore, we recommend that therapeutic drug monitoring and blood routine examination should be undergone for patients with long-term use of linezolid anti-infection therapy, especially those with liver insufficiency.

In conclusion, our findings speculated that the occurrence of thrombocytopenia and anemia was worth taking seriously during linezolid treatment. Proactive therapeutic drug monitoring of linezolid and blood routine examination may be beneficial either in preventing or in recovering from dose-dependent adverse events, making the management of long-term treatment more feasible and safer.

Limitation

We recognize that our study has some limitations. Firstly, Body Mass Index (BMI) was not included in the study for regression analysis as the height of the patient was not obtained. Then, the sample size was small, and a retrospective study may result in biased data. Besides, the medical records of leukopenia were missed in the study. Finally, it did not investigate the analysis of risk factors for linezolid-related anemia and associated linezolid-induced haematological toxicity. Therefore, the findings of this study need to be further verified by prospective randomized trials in multiple centers.

Declarations

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Contributions

We declare that all the listed authors have participated actively in the study and all meet the requirements of the authorship. Kai Mo, Hui Zhong and XiaoBu Lan designed the study and wrote the protocol. Wen Cao performed study. YanE Qin managed the sample collection. RuHua Wei, JuMan Li managed the literature searches and analyses. YingE Liang undertook the statistical analysis. YaTing Lu wrote the first draft of the manuscript. All authors approved the final manuscript.

Ethics declarations

Competing interests

All other authors have no competing interests to declare.

Additional information

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Tables

Table 1 Clinical characteristics of patients

Features	Value
Total; n	111
Gender(Male/Female); n(%)	76□68.47□/35□31.53□
Age (y)	64.0[49.5-76.5]
Body weight (kg)	60.0[50.0-67.0]
White blood cell ($\times 10^9$/L)	11.04[6.70-16.6]
Haemoglobin (g/L)	88.0[70.5-104.5]
Platelet count (10^9/L)	201[140-321]
ALT (U/L)	18[11-31]
AST (U/L)	25[16.5-36]
Total bilirubin (μmol/L)	8[5.6-16.55]
Total protein (g/L)	60.66±0.82
SCr (μmol/L)	89.0[61.5-144.0]
CCrC(mL/min)	56.87[32.46-84.12]
linezolid plasma trough concentration (mg/L)	5.84[3.16-10.95]
Administration period (d)	10.0[8.0-14.0]

Note: Data are expressed as numbers (%) for categorical variables and median [interquartile range] for continuous variables.

Table 2 Comparison of clinical characteristics between thrombocytopenia and no thrombocytopenia

Features	No-thrombocytopenia	Thrombocytopenia	P value
Gender(Male/Female); n(%)	45（70.3）/19（29.7）	31（66.0）/16（34.0）	0.682[a]
Age (y)	58.5[44.8-70.0]	75.0[55.5-84.0]	< 0.0001[b]
Body weight (kg)	60.0[50.8-68.0]	60.0[50.0-65.5]	0.482[b]
Platelet count (10^9/L)	201.5[137.0-319.3]	196.0[152.0-322.5]	0.957[b]
ALT (U/L)	19.5[13.8-32.8]	14.0[9.0-20.0]	0.010[b]
AST (U/L)	25.0[17.0-34.0]	26.0[16.0-39.5]	0.616[b]
Total bilirubin (μmol/L)	8.9[6.0-13.9]	7.9[5.2-21.1]	0.793[b]
Total protein (g/L)	60.59±1.03	60.80±1.38	0.741[c]
BUN (mmol/L)	5.70[4.15-11.00]	10.10[6.20-18.80]	0.002[b]
SCr (μmol/L)	76.5[57.0-100.0]	142.0[88.0-271.0]	< 0.0001[b]
CCr (mL/min)	69.28[56.68-100.06]	29.83[21.03-44.75]	< 0.0001[b]
linezolid plasma trough concentration (mg/L)	3.44[2.37-5.42]	12.31[7.99-16.89]	< 0.0001[b]
Administration period (d)	10.0[8.0-14.3]	10.0[8.0-14.0]	0.335[b]

a. Pearson chi-square test.

b. Mann–Whitney test.

c. Student's test.

Table3 Comparison of plasma trough concentrations in patients at the start of linezolid treatment.

Creatinine clearance	plasma trough concentrations(mg/L)
≥80	3.38[2.52-4.95]
50≤CCr<80	3.71[1.91-5.88]
30≤CCr<50	7.27[5.07-9.80]△
CCr<30	13.92[11.11-22.02]△

△Compared with normal group, P < 0.05.

Table 4 Multivariate regression analysis of variables associated with the occurrence of thrombocytopenia

Features	OR	95%CI	P value
Age (y)	1.042	0.418-8.125	0.271
Platelet count (10^9/L)	1.210	0.276-5.302	0.800
ALT (U/L)	1.137	0.014-90.890	0.954
AST (U/L)	2.713	0.097-76.261	0.558
CCr (mL/min)	5.463	1.249-23.888	0.024
Combined β-lactam antibiotics	0.397	0.077-2.053	0.271
linezolid plasma trough concentration (mg/L)	62.660	14.293-274.708	<0.001
Administration period (d)	1.927	0.389-9.554	0.422

Table 5 Comparison of clinical characteristics between anemia and no-anemia

Features	No-anemia	anemia	P value
Gender(Male/Female); n(%)	64（68.8）/29（31.2）	12（66.7）/6（33.3）	0.857[a]
Gender(Male/Female); n(%)	65.0[51.0-76.0]	59.0[45.8-77.3]	0.860[b]
Gender(Male/Female); n(%)	60.0[50.0-66.0]	62.0[50.0-69.5]	0.449[b]
Haemoglobin (g/L)	85.0[69.0-101.0]	100.0[87.3-115.0]	0.801[c]
ALT (U/L)	18.0[10.0-31.0]	18.5[13.0-34.3]	0.755[b]
AST (U/L)	25.0[16.0-34.0]	36.0[28.0-68.8]	0.008[b]
Total bilirubin (μmol/L)	7.7[5.4-12.7]	21.5[9.65-32.75]	0.012[b]
Total protein (g/L)	60.9±8.0	59.2±11.6	0.564[c]
BUN (mmol/L)	6.5[4.6-11.8]	12.9[10.6-21.4]	0.001[b]
SCr (μmol/L)	85.0[59.0-133.0]	171.5[96.8-289.8]	0.001[b]
CCr (mL/min)	59.88[38.87-91.24]	30.41[21.91-58.59]	0.005[b]
linezolid plasma trough concentration (mg/L)	5.12[2.91-8.90]	12.95[7.79-20.71]	0.001[b]
Administration period (d)	10.0[8.0-14.0]	8.5[7.3-12.8]	0.244[b]

a. Pearson chi-square test.

b. Mann–Whitney test.

c. Student's test.

Table 6 Multivariate regression analysis of variables associated with the occurrence of anemia

Features	OR	95%CI	P value
Age (y)	0.401	0.100-1.616	0.199
Haemoglobin (g/L)	0.317	0.094-1.074	0.065
ALT (U/L)	1.002	0.986-11.017	0.837
AST (U/L)	2.049	0.335-12.549	0.438
CCr (mL/min)	7.282	1.765-30.048	0.006
Combined β-lactam antibiotics	1.255	0.204-2.323	0.393
linezolid plasma trough concentration (mg/L)	6.364	1.937-20.910	0.002
Administration period (d)	0.545	0.131-2.269	0.405

Figures

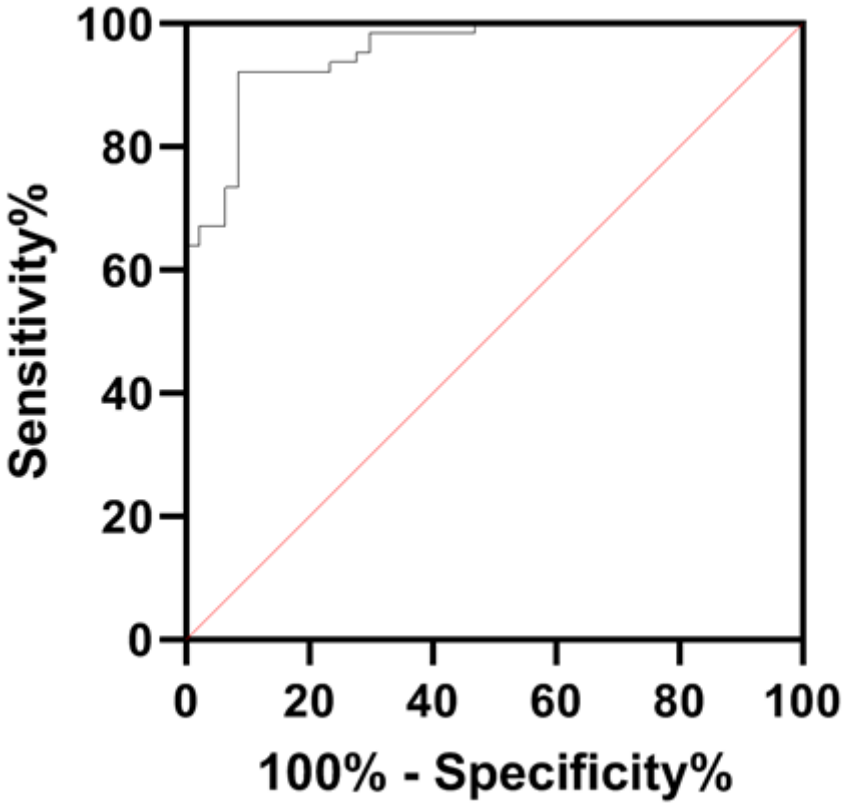

Figure 1

ROC curve of inezolidine-associated thrombocytopenia is shown using Logistic regression model to determine the probability.

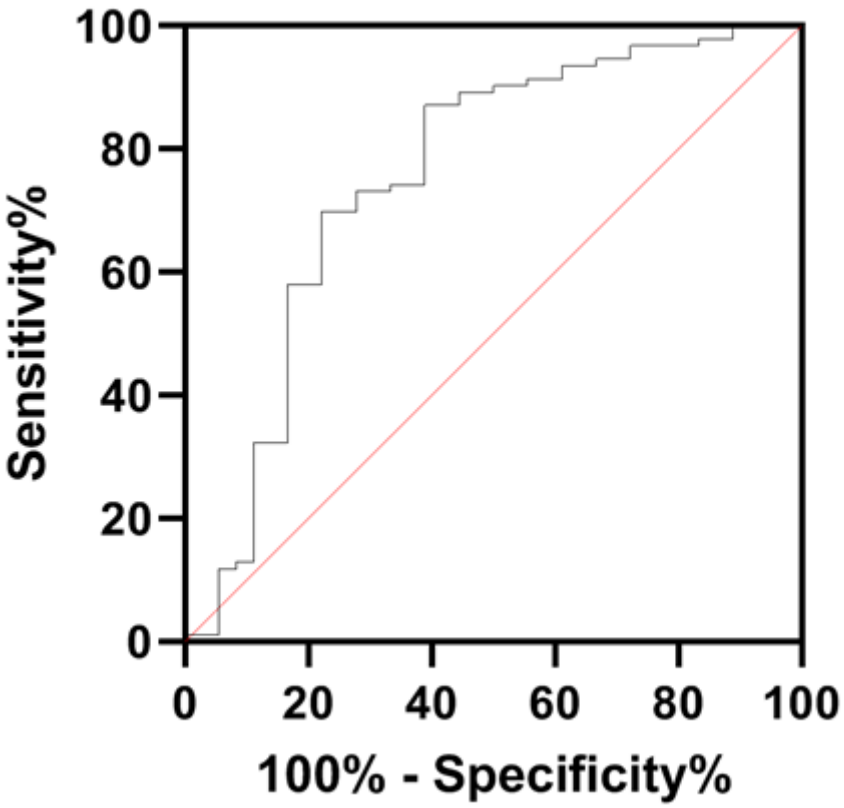

Figure 2

ROC curve of linezolidine-related hemoglobin decrease is shown using Logistic regression model to determine the probability.