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Original Article

Risk factors for linezolid - induced haematological toxicity in patients: a retrospective study

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Abstract

Introduction: This single-center, observational cohort study aimed to investigate the risk factors associated with linezolid-induced hematological toxicity by analyzing the linezolid trough concentration (Cmin) obtained from patients undergoing treatment between January 2020 and December 2021.

Methodology: A total of 111 eligible individuals were included in the study, of which 47 were diagnosed with linezolid-induced thrombocytopenia and 18 were diagnosed with linezolid-induced hemoglobin decrease.

Results: Binary logistic regression analysis revealed 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 Cmin > 7 mg/L (OR, 62.660; 95% CI, 14.293-274.708, $p = 0.001$) were risk factors associated with linezolid-induced thrombocytopenia. Area under the ROC curve for Cmin was 0.955, with a maximum Youden index of 0.837. The corresponding critical value was 6.94 mg/L (sensitivity 91.5%; specificity 92.2%). Ccr < 50 mL/min/1.73 m^2 (OR, 7.282; 95% CI, 1.765-30.048, $p = 0.006$) and Cmin > 7mg/L (OR, 6.364; 95% CI, 1.937-20.910, $p = 0.020$) were found to be associated with linezolid-induced hemoglobin reduction. The area under the ROC curve for Cmin was 0.755, Youden index was 0.477 at the maximum, and the corresponding critical value was 7.53 mg/L (sensitivity 77.8%; specificity 69.9%).

Conclusions: Renal insufficiency is a related risk factor for linezolid-induced hematological toxicity. Patients receiving linezolid treatment should be closely monitored with blood routine and plasma concentration, particularly in patients with moderate or severe renal insufficiency. The plasma trough concentration of linezolid could be a suitable predictor for linezolid-induced thrombocytopenia and anemia.

Key words: Linezolid; therapeutic drug concentration; thrombocytopenia; anemia.

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Introduction

Linezolid is the inaugural antibiotic of the oxazolidinone family and is extensively utilized for treating Gram-positive bacterial infections [1], notably methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Staphylococcus aureus* (VRSA), and vancomycin-resistant Enterococcus (VRE) [2-5]. Post-marketing clinical use of linezolid has reported hematologic impairments, encompassing anemia, leukopenia, and thrombocytopenia. Prior studies have indicated that specific risk factors may precipitate linezolid-induced hematological toxicity. These risk factors encompass renal impairment, chronic liver disease, prolonged linezolid therapy (> 14 days), and a low baseline platelet count [6-12]. However, the prescribing information suggests that pharmacokinetic parameters remain largely unaffected in patients with mild to moderate hepatic or renal insufficiency, negating the need for dosage adjustments. This stance contrasts with real-world studies [13]. In this study, we delved into potential risk factors linked to linezolid-induced hematological toxicity, aiming to mitigate these side effects and offer clinical guidance for drug safety.

Methodology

Patients

Data were gathered from hospitalized patients who received linezolid treatment for infection at a class-A tertiary hospital in Guangxi, spanning from January 2020 to December 2021. The inclusion criteria for this study were as follows: patients must have undergone linezolid therapy for a minimum duration of 4 days and had regular monitoring of plasma trough concentrations

throughout the treatment period. Conversely, the exclusion criteria encompassed incomplete clinical medical records, patients with pre-existing hematological diseases, individuals aged below 18 years, patients undergoing radiotherapy or chemotherapy for malignant tumors, and those with known allergies to linezolid.

Data collection

The data collection process was conducted utilizing the hospital information management system. With linezolid as the primary index, a total of 111 patients were ultimately included in the study, based on the inclusion and exclusion criteria retrieved from the medical and health electronic database of medication orders. The following basic patient characteristics were collected: gender, age, body weight, concurrent antibiotic usage, route and method of administration, duration of linezolid treatment, plasma trough concentration, and various laboratory data (including blood routine examination results, total protein concentration, albumin concentration, liver function indicators, kidney function indicators, and inflammatory parameters).

Determination of plasma trough concentration

The dosing regimen for patients was determined according to the package insert provided by the manufacturer of linezolid, which specified a dosage of 600 mg administered intravenously every 12 hours for a duration exceeding 3 days. Blood samples were collected 30 minutes prior to the administration of the subsequent dose, ensuring steady-state conditions. The concentration of linezolid in the plasma was measured using a validated high-performance liquid chromatography (HPLC) method. The observed linear range for linezolid concentration in plasma was between 0.35 and 50 mg/L, with a minimum detectable concentration of 0.05 mg/L. Both the intraday and interday accuracy and precision of this method were maintained within a 10% margin. Ethical approval for this study was granted by the ethics committee of the First People's Hospital of Nanning.

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]
CCr (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]

Data are expressed as numbers (%) for categorical variables and median [interquartile range] for continuous variables. ALT: Alanine aminotransferase; AST: Aspertate aminotransferase; SCr: Serum creatinine; Ccr: Creatinine clearance.

Assessment of haematological toxicity

The definitions of hematological toxicity were as follows: (1) Thrombocytopenia: a reduction of ≥ 25% in platelet count compared to the baseline level, or a platelet count ≤ 100×10^9/L; (2) Anemia: a decrease in hemoglobin value to 75% or less of the lower limit of normal (male < 120g/L, female < 110g/L), or a decrease of more than 25% from the baseline value; (3) Leukopenia: white blood cell count < 4×10^9/L. The baseline values were collected at the commencement of linezolid therapy. In cases where patient data for the first day of linezolid treatment were unavailable, the clinical data obtained prior to linezolid administration could be utilized as the baseline hematological parameters.

Statistical analysis

Data analysis was conducted using SPSS 23.0 software. For comparisons between two groups, enumeration data were expressed as percentages, while measurement data were expressed as mean ± standard deviation or median, respectively. Student's t-test was utilized for continuous variables with a normal distribution, and the Mann-Whitney U test was employed for variables that were not normally distributed. Pearson's χ^2 test was used for categorical variables. Furthermore, binary logistic regression analysis was performed to identify risk factors associated with linezolid-induced hematological toxicity. A p value < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curves were constructed based on relevant continuous variables in the multivariate analysis to predict clinical features.

Results

Characteristics of patients

Based on the established inclusion and exclusion criteria, a total of 111 patients were enrolled in this study. The male-to-female ratio was 76:35, with a median age of 64 years and a median weight of 60 kg. The median duration of linezolid treatment was 10 days. In this study, patients received intravenous

administration of linezolid at a dosage of 600 mg every 12 hours. The average linezolid concentration during the first therapeutic drug monitoring was 5.84 mg/L. Among the 111 patients, 47 (42.34%) developed thrombocytopenia, and 18 (16.22%) developed anemia following linezolid treatment. No cases of leukopenia were observed. The clinical characteristics of the patients are summarized in Table 1.

Assessment of thrombocytopenia

Among the 47 patients assessed for linezolid-related thrombocytopenia, significant differences were found in age ($p < 0.001$), alanine aminotransferase (ALT, $p = 0.010$), blood urea nitrogen (BUN, $p < 0.001$), serum creatinine (SCr, $p < 0.001$), creatinine clearance (Ccr, $p < 0.001$), and plasma trough concentration ($p < 0.001$) between patients with and without thrombocytopenia (Table 2).

The relationship between renal function and plasma trough concentration of linezolid was further investigated. The results revealed that the level of linezolid in patients with moderate and severe renal dysfunction was significantly higher than in those with normal renal function (Table 3).

The ROC curve based on the plasma trough concentration of linezolid is presented in Figure 1. The area under the curve was 0.955, with a maximum Youden index of 0.837. The corresponding critical value was 6.94 mg/L, which exhibited a sensitivity of 91.5% and a specificity of 92.2%.

A multivariate logistic regression analysis was conducted to identify risk factors for the development of thrombocytopenia. The following variables were included: age, ALT, aspartate aminotransferase (AST), baseline hemoglobin, glomerular filtration rate, and plasma trough concentration. Two independent risk factors for thrombocytopenia in patients receiving linezolid therapy were identified: Ccr < 50

Table 3. Comparison of plasma trough concentrations in patients at the start of linezolid treatment.

Creatinine clearance (mL/min)	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, $p < 0.05$. Ccr: Creatinine clearance.

Figure 1. ROC curve of inezolidine-associated thrombocytopenia is shown using Logistic regression model to determine the probability.

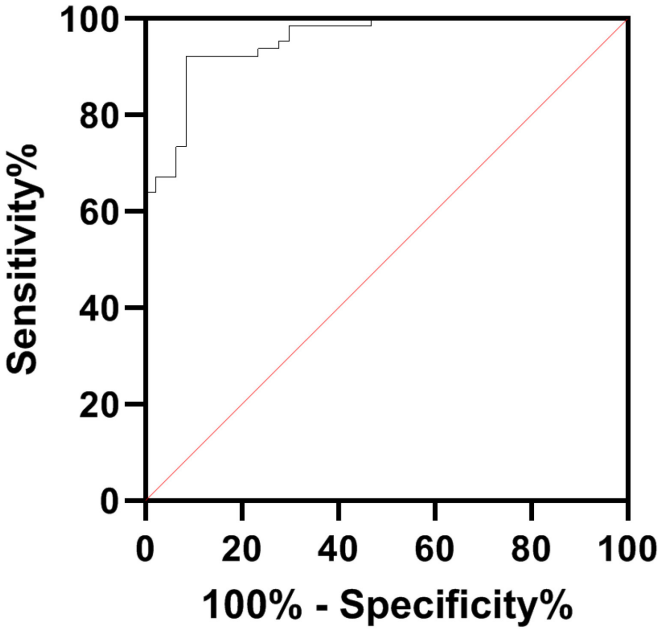

Table 2. Comparison of clinical characteristics between thrombocytopenia and no thrombocytopenia.

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]	< 0.001[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]	< 0.001[b]
CCr (mL/min)	69.28 [56.68-100.06]	29.83 [21.03-44.75]	< 0.001[b]
linezolid plasma trough concentration (mg/L)	3.44 [2.37-5.42]	12.31 [7.99-16.89]	< 0.001[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. ALT: Alanine aminotransferase; AST: Aspertate aminotransferase; BUN: Blood urea nitrogen; SCr: Serum creatinine; Ccr: Creatinine clearance.

mL/min/1.73 m² [OR, 5.463; 95% CI, 1.249-23.888; p = 0.024] and plasma trough concentration > 7 μg/mL [OR, 62.660; 95% CI, 14.293-274.708; p = 0.001]. The results are presented in Table 4.

Assessment of anemia

Among the 111 patients included in the study, 18 who received linezolid injections experienced anemia. Table 5 illustrates that several variables, including aspartate AST, total bilirubin, BUN, SCr, Ccr, and linezolid plasma trough concentration, were significant.

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

The binary logistic regression analysis revealed a significant correlation between linezolid-induced anemia and Ccr < 50 mL/min/1.73 m² [OR, 7.282; 95% CI, 1.765-30.048; p = 0.006], as well as linezolid plasma trough concentration > 7 μg/mL [OR, 6.364; 95% CI, 1.937-20.910; p = 0.020] after the elimination of confounding factors (Table 6).

Discussion

Although the mechanism underlying haematological toxicity during linezolid treatment remains unclear, previous studies have suggested a correlation with reversible bone marrow suppression [14,15] and immune mediation [16]. In our study, the incidence of linezolid-induced thrombocytopenia was 42.34%, and anemia was 16.22%. We speculate that the discrepancies between our findings and the prescribing information may be attributed to several limitations,

Figure 2. ROC curve of linezolidine-related hemoglobin decrease is shown using Logistic regression model to determine the probability.

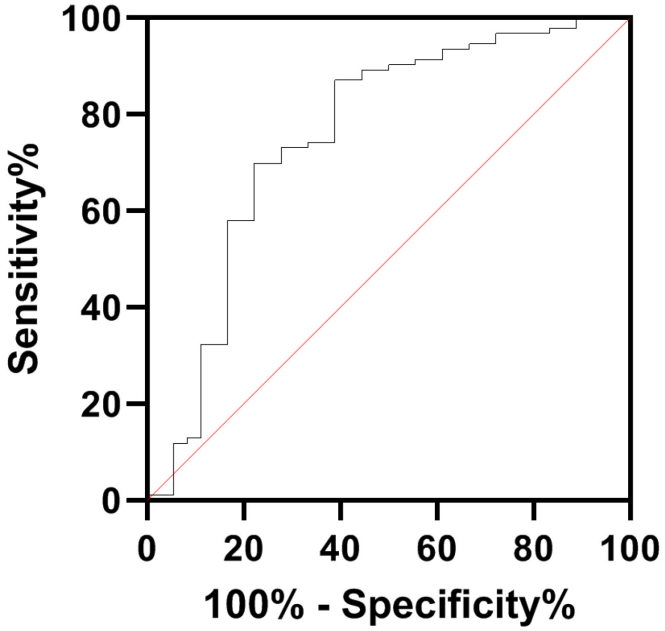

Table 4. Multivariate regression analysis of variables associated with the occurrence of thrombocytopenia

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

ALT: Alanine aminotransferase; AST: Aspertate aminotransferase; Ccr: Creatinine clearance.

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

Features	No-anemia	Anemia	*p*
Gender (Male/Female); n(%)	64 (68.8)/29 (31.2)	12 (66.7)/6 (33.3)	0.857[a]
Age (y)	65.0 [51.0-76.0]	59.0 [45.8-77.3]	0.860[b]
Body weight (kg)	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. ALT: Alanine aminotransferase; AST: Aspertate aminotransferase; BUN: Blood urea nitrogen; SCr: Serum creatinine; Ccr: Creatinine clearance.

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

ALT: Alanine aminotransferase; AST: Aspertate aminotransferase; Ccr: Creatinine clearance.

including the lack of unified standards for adverse reactions related to blood system damage, variations in research protocols, differences in the severity of the studied population, and the use of combination therapy during linezolid treatment.

Extensive data generated from studies involving both patients and animals have demonstrated that linezolid is well absorbed, with a mean absolute bioavailability close to 100%, and is rapidly distributed [17,18]. In vivo, two primary metabolites are produced by oxidation of the morpholine ring, resulting in two inactive open-ring carboxylic acid derivatives: the aminoethoxyacetic acid metabolite (PNU-142300) and the hydroxyethyl glycine metabolite (PNU-142586) [19]. These metabolites of linezolid are excreted into the urine [20]. According to the medicine label sheet for linezolid and some studies, pharmacokinetic parameters are not significantly altered in patients with renal insufficiency, and there is no need to adjust the dosage administered based on renal function [21]. However, in our study, poor renal function was identified as an independent risk factor for haematological toxicity during linezolid therapy, consistent with previous reports [22-25]. Despite administering a standard dose to each patient, we found that those with Ccr < 50 mL/min experienced higher incidences of linezolid-induced thrombocytopenia and anemia, as well as higher plasma trough concentrations, compared to those with normal Ccr at the start of treatment. Numerous studies have indicated that the risk of linezolid-related haematological toxicity is associated with a lower clearance rate of linezolid in patients with renal insufficiency and the resultant accumulation of linezolid metabolites [26]. Therefore, we recommend that the specification for linezolid may need to be augmented with recommendations for dosage adjustments in the presence of renal insufficiency to ensure patient safety.

The therapeutic window of linezolid is generally considered to be between 2-7 μg/mL [27,28]. In our study, we also identified that a trough level > 7 μg/mL was a significant risk factor for haematological toxicity in hospitalized adults. Specifically, we found that patients with haematological toxicity had higher trough levels compared to those without haematological toxicity. The ROC curve indicated critical trough concentration values of 6.94 μg/mL for thrombocytopenia and 7.53 μg/mL for anemia, respectively. Furthermore, for every 1 unit increase in trough concentration, the incidence of thrombocytopenia and anemia increased by 62.6 and 6.3 times, respectively. Therefore, we suggest that inpatients, especially those with moderate and severe renal insufficiency, should undergo therapeutic drug monitoring after achieving steady-state treatment with linezolid. Additionally, regular blood routine examinations should be performed during linezolid therapy to monitor for potential haematological toxicity. Proactive therapeutic drug monitoring could be especially helpful in personalizing linezolid therapy among patients.

Our study did not find an association between hepatic function indicators, such as total bilirubin, ALT, and AST, and the risk of thrombocytopenia. This differs from the findings of previous studies [29-31]. This apparent discrepancy may be due to the small number of patients with liver insufficiency in our study and the insignificant changes in liver function indicators observed in some patients with liver function impairment. The lack of a control arm and the limited sample size may also limit the generalizability of these findings. Further studies are needed to explore the relationship between these indicators and anemia. Therefore, we recommend that patients undergoing long-term linezolid therapy, especially those with liver insufficiency, undergo therapeutic drug monitoring and regular blood routine examinations to monitor for potential adverse events.

In conclusion, our findings suggest that the occurrence of thrombocytopenia and anemia should be taken seriously during linezolid treatment. Proactive therapeutic drug monitoring and regular blood routine examinations can help prevent or manage dose-dependent adverse events, ensuring the feasibility and safety of long-term treatment.

Limitations

We acknowledge several limitations in our study. Firstly, we were unable to include Body Mass Index (BMI) in the regression analysis due to the absence of patient height data. Secondly, the sample size was relatively small, and the retrospective nature of the study may introduce biased data. Additionally, the medical records did not include information on leukopenia, which may limit our understanding of this aspect. Furthermore, our study did not investigate the analysis of risk factors for linezolid-related anemia and other linezolid-induced haematological toxicity. As such, further validation of our findings is warranted through prospective randomized trials conducted across multiple centers.

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Authors' Contributions

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

Ethics approval and consent to participate

The study was reviewed and approved by the Medical Ethics Committee of The First People's Hospital of Nanning, in accordance with the Declaration of Helsinki and the ethical requirements for biomedical research promulgated by China. As this was a retrospective study, informed consent was not obtained from patients and was waived by the Medical Ethics Committee of The First People's Hospital of Nanning. All ethical and professional considerations were followed, and particular attention was paid to keeping patient details in strict confidence. Data was analyzed and disseminated anonymously.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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