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Prevalence of potential drug-drug interactions among intensive care unit patients receiving linezolid: a cross-sectional study

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Abstract. – OBJECTIVE: Linezolid is commonly used in intensive care units (ICU) but has the potential to interact with other drugs. This study aimed to evaluate the prevalence of potential drug-drug interactions in ICU patients receiving linezolid.

PATIENTS AND METHODS: Data of ICU patients receiving linezolid were extracted and included in the Hospital Prescription Analysis Program of China, and the risk of potential drug-drug interactions between concomitant drugs and linezolid was evaluated using the Lexicomp database.

RESULTS: A total of 3,712 ICU patients from 59 hospitals were included in the analysis, and patients received an average of 17 concomitant drugs. A total of 67.9% of patients had potential drug-drug interactions. Patients receiving concomitant drugs with risk ratings of "X", "D", and "C" categories were 20.8%, 30.4%, and 35.1%, respectively. Opioids were the most frequently prescribed drug class with drug-drug interactions (DDIs) in the "X" category, whereas butorphanol, metoclopramide, and sufentanil were the most contraindicated concomitant drugs.

CONCLUSIONS: ICU patients receiving linezolid have a high prevalence of potential drug-drug interactions, and efforts should be made to better recognize and manage this risk.

Key Words:
Linezolid, Drug-drug interaction, Serotonin, Opioid.

Introduction

Linezolid is the first member of the oxazolidinone class of antibiotics to show good activity against Gram-positive bacteria, including methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus*[1]. It has favorable clinical outcomes for the treatment of severe infections and is commonly used in patients admitted to intensive care units (ICUs)[2]. However, ICU patients receive numerous drugs simultaneously, and linezolid exhibits drug-drug interactions (DDIs) with some drugs[3]. It can exhibit a nonspecific inhibitory effect on monoamine oxidase and may cause life-threatening serotonin toxicity when combined with serotonergic drugs, including selective serotonin reuptake inhibitors, opioids, and tricyclic antidepressants[4]. However, the risk of interaction of drugs with linezolid has always been neglected in clinical practice, and data regarding this issue are limited. Therefore, we conducted this cross-sectional study to determine the prevalence of potential DDIs in ICU patients receiving linezolid.

Patients and Methods

Study Design and Ethical Approval

This was a cross-sectional study. Ethical approval for the study was obtained from the Ethics Committee of Sir Run Run Shaw Hospita, College of Medicine, Zhejiang University (KEYAN20210924-33). Owing to the retrospective nature of the study, the need for informed consent was waived in accordance with local regulations.

Patient Inclusion and Data Collection

Data of patients were extracted from a large prescription database, the Chinese Hospital Prescription Analysis Project, which is widely used in China[5-9]. The database contained the prescription information of patients at the participating hospital. Patients who met the following crite-

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ria were included: (1) patients admitted to the ICU, (2) patients admitted to hospitals located in six major areas of China (Beijing, Shanghai, Hangzhou, Tianjing, Guangzhou, and Chengdu), and (3) patients receiving linezolid (as tablets or injections). This study was restricted to collecting patient information for 40 random sampling days in 2019 (**Supplementary Table I**), and the data on drugs administered to the patients on the sampling days were extracted. The following items were included in the prescription information: patient ID, age, sex, diagnosis, hospital ID, admission department, generic drug name, formulation, and dosing regimen. Patients were excluded if their prescription information was incomplete.

Analysis

The demographic characteristics of the included patients were descriptively analyzed. The number and class (according to the ATC index) of the concomitant drugs in each patient were counted and analyzed. Drugs with local effects, water injection, glucose injection, and sodium chloride injection were not included in the analysis. The risk of potential DDIs between linezolid and concomitant drugs was evaluated using the Lexicomp database. This database categorizes the DDIs into five categories, three of which are considered clinically meaningful: X (combination to be avoided), D (therapy modification to be considered), and C (therapy to be monitored). The prevalence of DDIs involving linezolid was presented as the percentage of patients with any grade of clinically meaningful DDI. The data were processed using the Access software.

Results

Patient Demographics

A total of 3,712 ICU patients from 59 hospitals were included in the analysis. Demographic details are presented in Table I. Nearly half of the patients were older adults (>65 years), and 68.5% were males.

Concomitant Drugs

In this study, 925 drugs were co-administered to patients receiving linezolid. Patients received an average of 17 drugs, and as shown in Table I, 78.8% of the patients received more than 10 drugs. The most common concomitant drugs are listed in Table II.

Table I. Patient demographic characteristics and prevalence of potential drug-drug interactions involving linezolid.

Patient characteristic	N (%)
Sex	
Male	2,542 (68.48)
Female	1,170 (31.52)
Age (year)	
≤8	251 (6.76)
9-18	58 (1.56)
19-65	1,637 (44.1)
66-75	749 (20.18)
>75	1,017 (27.4)
Concomitant drugs[a]	
≤10	785 (21.15)
11-20	1,813 (48.84)
21-30	975 (26.27)
>30	139 (3.74)
Level of DDI risk[b]	
Any	2,520 (67.89)
1[c]	1,133 (30.52)
2[c]	727 (19.59)
3 and more[c]	660 (17.78)
X	772 (20.8)
D	1,130 (30.44)
C	1,302 (35.08)

[a]Drugs with local effect, water for injection, glucose injection, and sodium chloride injection were not treated as concomitant drugs.
[b]Level of DDI risk was evaluated using Lexicomp database.
[c]This indicated the number of DDI risk of patients.

DDI Risk

We used the Lexicomp database to screen for potential DDIs and identified 4,953 potential DDI events. Overall, 67.9% of patients had potential DDIs. The proportions of patients receiving con-

Table II. Ten most frequently prescribed drugs combined with linezolid.

Name	ATC code	Patients
Ambroxol hydrochloride	R05CB06	2,508
Potassium chloride	B05XA01	1,816
Meropenem	J01DH02	1,204
Furosemide	C03CA01	1,152
Albumin	B05AA01	1,105
Budesonide	R03BA02	995
Pantoprazole	A02BC02	988
Heparin sodium	B01AB01	828
Norepinephrine	C01CA03	814
Insulin	A10AC01	806

comitant drugs with "X", "D", and "C" categories of DDI risk were 20.8%, 30.4%, and 35.1%, respectively. Details of the "X" category of potential DDI events are shown in Table III, and the "D" and "C" categories of potential DDI events are shown in **Supplementary Table II**. All drugs with DDI risk in the "X" category were serotonergic, and opioids were the most frequently prescribed class. The most common contradictory concomitant drugs were butorphanol, metoclopramide, and sufentanil.

Discussion

To the best of our knowledge, this is the first study to evaluate the prevalence of potential DDIs among ICU patients receiving linezolid. As the patients were numeric and from 59 hospitals in China, the results are nationally representative. We found that the prevalence of potential DDIs in patients receiving linezolid was high and that the most frequently prescribed

Table III. Concomitant drugs with risk of "X" category of interaction with linezolid.

Name	ATC code	Patients	Severity	Reliable rating	Reason
Metoclopramide	A03FA01	229	Moderate	Fair	Metoclopramide may enhance the hypertensive effect of Monoamine Oxidase Inhibitors.
Sufentanil	N01AH03	174	Major	Fair	Sufentanil may enhance the adverse/toxic effect of Monoamine Oxidase Inhibitors.
Morphine	N02AA01	50	Moderate	Fair	Monoamine Oxidase Inhibitors may enhance the adverse/toxic effect of Morphine (Systemic).
Hydromorphone	N02AA03	2	Moderate	Fair	Monoamine Oxidase Inhibitors may enhance the adverse/toxic effect of Hydromorphone.
Oxycodone	N02AA05	1	Moderate	Fair	Oxycodone may enhance the serotonergic effect of Monoamine Oxidase Inhibitors. This could result in serotonin syndrome.
Butorphanol	N02AF01	330	Moderate	Fair	Butorphanol may enhance the serotonergic effect of Monoamine Oxidase Inhibitors.
Metamizole sodium	N02BB02	1	Major	Fair	Dipyrone may enhance the adverse/toxic effect of Myelosuppressive Agents.
Carbamazepine	N03AF01	11	Major	Fair	Carbamazepine may enhance the adverse/toxic effect of Monoamine Oxidase Inhibitors.
Selegiline	N04BD01	1	Major	Fair	Linezolid may enhance the serotonergic effect of Monoamine Oxidase Inhibitors (Type B).
Fluoxetine	N06AB03	9	Major	Good	Linezolid may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors.
Citalopram	N06AB04	3	Major	Good	Linezolid may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors.
Sertraline	N06AB06	3	Major	Good	Linezolid may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors.
Escitalopram	N06AB10	7	Major	Good	Linezolid may enhance the serotonergic effect of Selective Serotonin Reuptake Inhibitors. This could result in serotonin syndrome.
Trazodone	N06AX05	3	Major	Good	Linezolid may enhance the serotonergic effect of Serotonergic Non-Opioid CNS Depressants.
Mirtazapine	N06AX11	5	Major	Good	Linezolid may enhance the serotonergic effect of Serotonergic Non-Opioid CNS Depressants.
Codeine	R05DA04	3	Moderate	Fair	Monoamine Oxidase Inhibitors may enhance the adverse/toxic effect of Codeine.
Methylene blue	-	19	Major	Good	Methylene Blue may enhance the serotonergic effect of Linezolid.

The level of drug-drug interaction risk with linezolid were evaluated using Lexicomp Database, as well as the severity, reliable rating, and reason.

drugs were opioids. This highlights the need for special attention to the risk of DDIs when prescribing linezolid.

Polypharmacy was common in this study, and patients received numerous drugs simultaneously. A previous study[10] also found that polypharmacy was prevalent in pediatric ICUs and raised concerns about potential DDI risks. It has been reported that 75% of patients experience some level of potential DDIs, and 6% have more than one potential DDI. Another study[11] focusing on adult ICU patients found a high prevalence (69.7%) of DDIs, and the number of co-used drugs significantly increased the DDI risk. Our study found a similar prevalence of all DDIs in patients who received linezolid but a higher prevalence of contraindicated DDIs. Reducing the number of drugs and withdrawing unnecessary drugs would help lower the DDI risk.

Among the ten most commonly used concomitant drugs, only norepinephrine had a risk of "D" category of DDI event. This is because linezolid enhances the hypertensive effects of sympathetic drugs. However, this risk could be addressed in patients admitted to the ICU. Norepinephrine is infused as a vasopressor to treat vasodilatory shock[12]. Blood pressure is closely monitored, and the norepinephrine dose is adjusted according to the reaction[12]. Therefore, the specificity of ICU patients should be considered when evaluating the risk of developing a DDI.

It is not surprising that opioids are the most frequently prescribed drugs, as most ICU patients require sedation and analgesic therapy due to pain or invasive intervention[13]. The most widely accepted tool for the diagnosis of serotonin syndrome (SS) is the Hunter serotonin toxicity criteria[14]; however, it is difficult to apply this tool and rule out all SS in ICU patients because of their complicated illness. Although it was found that the occurrence of severe SS in ICU patients who received concomitant linezolid and opioids was low, SS due to the concomitant use of linezolid and opioids, including fentanyl and morphine, was observed and reported in a series of cases[15-18]. Butorphanol, an opioid analgesic and less addictive opioid with unique pharmacological profiles, was the most commonly used drug with DDIs in the "X" category in this study[19]. This may be due to the increased use of butorphanol in the ICU. Butorphanol can also interact with linezolid, similar to other opioids, despite the lack of relevant reports. Therefore, physicians should be cautious when prescribing linezolid.

The main limitation of this study was that the DDIs were evaluated based on a database, and the outcome of DDI with linezolid was not investigated. Moreover, evidence regarding the DDI potential of linezolid and concomitant drugs needs to be re-examined.

Conclusions

This study evaluated the prevalence of potential DDIs in ICU patients receiving linezolid. Polypharmacy was common in the study population, and 78.8% of patients received more than 10 drugs simultaneously. We found that 67.9% of patients had potential DDIs with linezolid, and 20.8% of patients had received contraindicated concomitant drugs. Opioids were the most frequently prescribed contraindicated concomitant drug class. Special attention should be paid to DDIs in ICU patients receiving linezolid, and efforts should be made to better recognize and manage the risks of potential DDIs.

Authors' Contributions

Conceptualization, ZY, YZ; Data curation, HJ, LY; Formal analysis, HJ, LY, XW; Funding, JY; Investigation HJ, LY, XW; Methodology HJ, LY, ZY; Project administration, ZY, YZ; Resources, HJ, YZ; Supervision, ZY, YZ; Validation, HJ, LY; Visualization, HJ, LY; Roles/Writing - original draft, HJ, LY; Writing - review and editing, ZY.

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Availability of Data and Materials

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

Ethics Approval

The study was approved by the Ethics Committee of Sir Run Run Shaw Hospital, College of Medicine, Zhejiang University (KEYAN20210924-33).

Informed Consent
Informed consent was waived due to the nature of the study.

Conflict of Interest
The authors declare no conflict of interest.

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