Efficacy and Safety of Linezolid in Treating Gram-Positive Bacterial Infection in the Elderly: A Retrospective Study

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Abstract Linezolid is commonly used for the treatment of drug-resistant Gram-positive bacterial infection. This study aimed to evaluate the efficacy and safety of linezolid in treating Gram-positive bacterial infection in the elderly from January 2010 to December 2012. Total 40 elderly patients (>60 years old) with Gram-positive bacterial infection were treated with linezolid and their demographic and clinical data were collected and analyzed. Among the 40 patients, 31 patients (77.5 %) were cured. Linezolid caused little adverse effects on liver and renal function. The main adverse effect was thrombocytopenia and its incidence was significantly associated with baseline platelet count and the duration of treatment ($P < 0.05$). Logistic regression analysis showed that the baseline platelet count $<200 \times 10^6/\text{mL}$, but not the age, the sex, the length of hospital stay, baseline levels of hemoglobin, alanine aminotransferase, or creatinine clearance rate was significantly associated with linezolid-induced thrombocytopenia. In conclusion, linezolid is effective to cure Gram-positive bacterial infection in the elderly and causes little adverse effects on liver and renal function. Timely monitoring of baseline platelet count may be helpful to guide the use of linezolid to avoid the occurrence of thrombocytopenia.

Keywords Linezolid · Gram-positive bacteria · Elderly · Thrombocytopenia · Platelet count

Introduction

Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) are major pathogens of hospital-acquired infections. More importantly, community-acquired infections due to MRSA have become increasingly problematic in recent years [1, 2]. Linezolid is an oxazolidinone antibiotic with good activity against drug resistant Gram-positive bacteria such as MRSA [3–5]. The mechanism of action of linezolid involves the inhibition of bacterial protein synthesis through binding to the domain V regions of the 23 S rRNA gene [6]. Resistance to linezolid requires mutations of multiple gene copies, and thus linezolid seldom induces drug resistance of bacteria [7]. Linezolid is metabolized via morpholine ring oxidation. In humans, ~30 % of a linezolid dose is excreted in the urine as the parent drug [3]. However, linezolid has been reported to cause serious adverse effects such as thrombocytopenia, which can be ameliorated or prevented by co-administration of Vitamin B6 [3, 8]. The other adverse effects included nausea, diarrhea, vomiting, headache, tongue discoloration and oral monilia [9].

Old people have significantly high chance to be hospitalized due to their medical conditions and are more susceptible to hospital-acquired infections, especially those caused by MRSA. Currently, no studies have evaluated the efficacy and safety of linezolid in the treatment of Gram-positive bacterial infection in elderly patients. Therefore, this study aimed to evaluate the efficacy of linezolid in the treatment of elderly patients with Gram-positive bacterial

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infection. Furthermore, we examined the adverse effects of thrombocytopenia in these patients.

Materials and Methods

Patients

Total 40 patients with Gram-positive bacterial infection who visited Yantai Hill Hospital between January 2010 and December 2012 were enrolled in this study, which was approved by the Ethics Committee of Yantai Hill Hospital. Data of the patients were extracted from their medical records. Among 40 patients, 20 cases had respiratory tract infection, 10 cases had skin and soft-tissue infection, 2 cases had blood stream infection, and 8 cases had infection at other sites. The most commonly isolated pathogen was *S. aureus* (17 cases), followed by *Staphylococcus epidermidis* (10 cases), *Staphylococcus lugdunensis* (5 cases), *Enterococcus faecalis* (3 cases), *Staphylococcus capitis* (2 cases), *Staphylococcus haemolyticus* (2 cases), and *Staphylococcus hominis* (1 case).

Treatment

All patients were treated with linezolid at the dose of 600 mg by i.v. infusion for at least 7 days. Mean duration of treatment was 12 days (range 7–20 days).

They were divided into three groups based on the response to linezolid treatment: cure, failure, or indeterminate outcome. Cure outcome indicated the resolution of the symptoms of infection and no progression after 7 days of therapy; failure outcome indicated persistence or even progression of the symptoms of infection after 7 days of therapy; and indeterminate outcome indicated that the situation was between cure and failure outcome.

Evaluation of Thrombocytopenia

The platelet count was tested in each patient each day since the beginning of linezolid therapy, for three times for each sample. Thrombocytopenia was defined as a platelet count below $50 \times 10^6/\text{mL}$. The patients were divided into two groups according to the occurrence of thrombocytopenia. The following clinical characteristics were collected and compared in the thrombocytopenia group and the non-thrombocytopenia group: age, sex, length of hospital stay, baseline alanine aminotransferase (ALT) and creatinine clearance rate (CCr), baseline hemoglobin (HGB) concentration and platelet count, and duration of linezolid treatment.

Statistical Analysis

Data were presented as mean $\pm$ SD and analyzed using SPSS version 13.0 package (SPSS Inc., Chicago, IL, USA). Continuous data were analyzed by unpaired Student's *t* test while categorical data were analyzed by Fisher's test. Risk factors associated with thrombocytopenia were analyzed by logistic regression analysis. $P < 0.05$ was considered as statistically significant.

Results

Clinical Characteristics of the Patients

Total 40 patients were enrolled in the study. They included 26 men and 14 women, the mean age was 78 years old (age range 60–95 years). All patients received linezolid treatment at the dose of 600 mg by IV infusion. Mean duration of treatment was 12 days (range 7–20 days). The clinical characteristics of the patients were listed in Table 1. Among the 40 patients, 31 patients (77.5 %) were cured. Three patients died after treatment because of severe illnesses accompanied by respiratory and circulation failure.

To evaluate the potential adverse effects of linezolid, we compared the platelet count, hemoglobin concentration, liver and renal function and CCr in all patients before and after linezolid treatment. The results showed that the

Table 1 Clinical characteristics of the patients ($n = 40$)

Clinical condition	<i>n</i>	Percentage
Site of infection		
Respiratory infection	20	50
Skin and soft tissues	10	25
Blood stream infection	2	5
Other sites	8	20
Organisms		
<i>Staphylococcus aureus</i>	17	42.5
<i>Staphylococcus epidermidis</i>	10	25
<i>Staphylococcus lugdunensis</i>	5	12.5
<i>Enterococcus faecalis</i>	3	7.5
<i>Staphylococcus capitis</i>	2	5
<i>Staphylococcus haemolyticus</i>	2	5
<i>Staphylococcus hominis</i>	1	2.5
Clinical characteristics		
Mechanical ventilation	20	50
Hematological disease	2	5
Renal inadequacy	12	30
Age >70 years old	35	87.5
Length of stay >30 days	29	72.5
ICU admission	32	80

platelet count was significantly decreased after treatment ($P < 0.05$), while other indexes such as hemoglobin concentration, liver and renal function showed no significant differences before and after treatment ($P > 0.05$, Table 2). Furthermore, in the 12 patients with renal dysfunction, renal function did not get worse and even got improved in some patients after linezolid treatment. These results suggest that the main adverse effect of linezolid is thrombocytopenia but not liver or renal dysfunction in the elderly patients.

Potential Risk Factors Associated with the Occurrence of Thrombocytopenia

Because thrombocytopenia was a major adverse effect after linezolid treatment, we analyzed the risk factors associated with the occurrence of thrombocytopenia in elderly patients after linezolid treatment. We divided the patients into two groups based on the occurrence of thrombocytopenia and compared the characteristics of the patients in these two groups.

The duration of linezolid treatment was 15.2 ± 2.3 days in patients with thrombocytopenia, significantly longer than in patients without thrombocytopenia (11.7 ± 1.9 days) ($P < 0.05$). In contrast, the baseline platelet count was significantly lower in patients with thrombocytopenia than in patients without thrombocytopenia ($195 \pm 97 \times 10^6/\text{mL}$ vs. 272 ± 101 , $P < 0.05$). However, other factors such as the age, the sex, the length of hospital stay, baseline levels of hemoglobin, ALT, and CCr showed no significant difference between the two groups ($P > 0.05$). Based on this, we performed logistic regression analysis and found that the baseline platelet count $<200 \times 10^6/\text{mL}$ was significantly associated with the occurrence of thrombocytopenia in elderly patients after linezolid treatment (OR = 0.35; 95 % CI = 0.07–0.95; $P < 0.05$). These data suggest that low baseline platelet count is a risk factor for the development of thrombocytopenia after linezolid treatment.

Table 2 Comparison of blood, liver and renal function in the patients ($n = 40$) before and after linezolid treatment

Indexes	Value before treatment	Value after treatment	<i>P</i>
Platelet ($\times 10^6/\text{mL}$)	220 ± 84	132 ± 55	0.01
Hemoglobin (g/L)	99 ± 21	94 ± 18	0.52
ALT (U/L)	31 ± 25	25 ± 18	0.41
AST (U/L)	42 ± 25	40 ± 23	0.98
CCr (mL/min)	56 ± 35	51 ± 33	0.73

ALT alanine aminotransferase, AST aspartate aminotransferase, CCr creatinine clearance rate

Discussion

Gram-positive bacteria, especially MRSA, are known as the most common causes of hospital and community acquired infection [10]. Linezolid is the first oxazolidinone approved for clinical use for Gram-positive bacteria infection. Linezolid blocks the initiation, the first step of protein synthesis, while most other protein synthesis inhibitors inhibit the elongation in the process of protein synthesis. Therefore, the cross-resistance between linezolid and other protein synthesis inhibitors is very uncommon, and linezolid induced drug resistance in bacteria is seldom reported. Consequently, linezolid has become the recommended choice for the treatment of hospital and community acquired infection [11]. However, the use of linezolid in the elderly with hospital and community acquired infection is seldom reported, and its efficacy and safety in these patients are not clear.

In this study, we collected and analyzed the clinical data from 40 elderly patients who were treated with linezolid for Gram-positive bacteria infection. Our results showed that linezolid was efficient in the treatment of Gram-positive infection and the total clinical efficacy achieved 77.5 %. However, we found that there was no direct link between the types of organism or site of infection with the success or failure with linezolid treatment.

Notably, in this study we found that the use of linezolid induced the main adverse effect of thrombocytopenia. To identify the potential risk factors associated with the development of thrombocytopenia, we divided the patients into two groups based on the occurrence of thrombocytopenia after linezolid treatment. By univariate analysis, we found that the duration of linezolid treatment was significantly longer and the baseline platelet count was significantly lower in patients who developed thrombocytopenia than in those who did not develop thrombocytopenia. Furthermore, by logistic regression analysis, we found that the baseline platelet count $<200 \times 10^6/\text{mL}$ was significantly associated with the development of thrombocytopenia in elderly patients after linezolid treatment. Thrombocytopenia was reported to occur only after linezolid treatment for 14 days, suggesting that the development of thrombocytopenia is associated with the accumulation of linezolid in the body [12]. However, in this study our results showed that the duration of linezolid treatment (>14 days) was not significantly associated with the occurrence of thrombocytopenia after logistic regression analysis. These inconsistent results may be due to the differences in the patient population and the short duration we chose in this study.

On the other hand, we found that the occurrence of thrombocytopenia was not significantly associated with other factors such as the age, the sex, the length of hospital stay, baseline levels of hemoglobin, alanine aminotransferase, and CCr. These results suggest that these factors are not the risk factors for linezolid-induced thrombocytopenia in the elderly

patients. However, the number of cases in this study is small, and future studies that enroll large-scale patients are needed to confirm our findings, which will help identify the risk factors associated with the development of thrombocytopenia in elderly patients after linezolid treatment.

To our knowledge, this is the first study that evaluated the efficacy and safety of linezolid in treating Gram-positive bacterial infection in the elderly. Linezolid is effective to cure Gram-positive bacterial infection and causes little adverse effects on liver and renal function. The main adverse effect is thrombocytopenia and its incidence is associated with baseline platelet count and the duration of treatment. Moreover, the baseline platelet count $<200 \times 10^6/\text{mL}$ is a significant risk factor for linezolid-induced thrombocytopenia. These results suggest that timely monitoring of baseline platelet count may be helpful to guide the use of linezolid in treating Gram-positive bacterial infection in the elderly to avoid the occurrence of thrombocytopenia.

Conflict of interest None.

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