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Reduction of linezolid-associated thrombocytopenia by the dose adjustment based on the risk factors such as basal platelet count and body weight☆,☆☆

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ABSTRACT

The aim of the present study was to evaluate the efficacy of dose modification based on the risk factor for linezolid-induced thrombocytopenia. A multivariate logistic regression analysis performed in the observational study showed that low body weight of <55 kg (odds ratio [OR]: 33.2, 95% confidence interval [CI]: 2.16–510.1, $P = 0.012$) and the baseline platelet count of $<200 \times 10^3/mm^3$ (OR: 24.9, 95% CI: 1.53–404.7, $P = 0.024$) were found to be risk factors for linezolid-induced thrombocytopenia. In the subsequent intervention study, in which daily dose of linezolid was set to 20 mg/kg in patients with either one of the risk factors or 1200 mg in those without any risk factor, the onset of thrombocytopenia was significantly prolonged in the intervention study group ($P = 0.043$), without reducing clinical efficacy. These findings suggest that dose adjustment of linezolid is effective in preventing thrombocytopenia without reducing its clinical efficacy in patients having risk factors.

1. Introduction

Linezolid is the first oxazolidinone antibiotic agent with a broad spectrum of activity against many Gram-positive bacteria, including resistant strains of several species, such as methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant pneumococci, and vancomycin-resistant enterococci (Fung et al., 2001). Linezolid inhibits the initiation phase of protein synthesis in microorganisms by binding to domain V of the 23S ribosomal RNA of the 50S subunit of bacterial ribosomes. This agent shows high tissue penetration and is available in both intravenous and oral forms, since it is rapidly absorbed with an almost 100% bioavailability (Dryden, 2011). However, linezolid is associated with reversible myelosuppression, including thrombocytopenia and anemia. Data from 2046 linezolid-treated and 2001 comparator-treated patients indicated that the incidence of thrombocytopenia (>25% decrease in platelet count) was 2.9% in linezolid-treated patients compared to 1.6% in comparator-treated group (Gerson et al., 2002). On the other hand, the incidence rate of linezolid-induced thrombocytopenia varies ranging from 1.9% to 17.1% (Birmingham et al., 2003; Falagas et al., 2008; Sotgiu et al., 2012).

We reported previously that the incidence of linezolid-induced thrombocytopenia was 17% (7/42 patients) and that high dose (≥22 mg/kg) was the risk of linezolid-induced thrombocytopenia (Niwa et al., 2009).

In the present study, we prospectively examined the effect of the modification of the daily dose of linezolid based on the risk factors that were analyzed in a separate retrospective study on the safety and efficacy of this agent.

2. Materials and methods

2.1. Patients and study design

Patients who received linezolid injections at a daily dose of 1200 mg during June 1, 2006, and March 31, 2009, in Gifu University Hospital were the subject of the present observational study, while those receiving the same injections during October 1, 2009, and March 31, 2012, were enrolled in the subsequent intervention study. In our hospital, the use of linezolid is strictly limited to physicians who obtained an approval from the infection control team (ICT). Data were extracted from electronic medical records kept in a central database in our hospital. Medical charts without patient names and identification numbers were stored in a Microsoft Excel file.

Patients received intravenous linezolid solution at a daily dose of 1200 mg (600 mg, q12h) in the observational study. Both univariate and multivariate logistic regression analyses were carried out in 50 patients to determine the risk factor for linezolid-associated thrombocytopenia.

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In the intervention study, ICT members checked the presence or absence of risk factors for linezolid-induced thrombocytopenia, when they received an application form to use linezolid injection from physicians. The ICT members recommended the body weight-adjusted daily dose of 20 mg/kg, if the patient had risk factors for thrombocytopenia. Unless patients had any risk factor, the daily dose of linezolid was suggested to be 1200 mg (600 mg, q12h). The incidence of thrombocytopenia, which was a primary endpoint, was compared between the intervention study group and the observational study group. The onset time of thrombocytopenia was also compared between the 2 groups as the secondary endpoint.

To avoid the influence of other drugs or disease states that affect bone marrow function on the platelet count, patients receiving platelet transfusion or taking any medicines that affect platelet counts, including anticancer drugs, before or during the linezolid treatment were excluded from the present study.

2.2. Risk analysis for thrombocytopenia

Thrombocytopenia was defined as the decrease in platelet count of ≥25% and a final count of $<100 \times 10^3/mm^3$ according to the previous studies with minor modifications (Rao and Hamilton, 2007; Soriano et al., 2007). Creatinine clearance was estimated from serum creatinine according to the Cockcroft-Gault equation (Cockcroft and Gault, 1976).

Both univariate and multivariate logistic regression analyses were carried out to determine risk factors for linezolid-associated thrombocytopenia in 50 patients who received linezolid injection for at least 3 days.

2.3. Clinical efficacy

The rates of clinical failure and re-infection at 30 days after completion of the treatment were measured to evaluate the clinical efficacy of linezolid. Clinical failure was defined as inadequate response to linezolid therapy for Gram-positive bacteria, including 1) the need for a change to another anti-MRSA agent, 2) a positive culture reported at the end of linezolid therapy, and 3) death associated with Gram-positive bacterial infection, according to the previous reports with a minor modification (Sakoulas et al., 2009; Raad et al., 2004). Inadequate response due to Gram-negative bacterial or viral infection was excluded.

Thirty-day re-infection was defined as infection caused by the same strain of Gram-positive bacteria with the same susceptibility at the same infected site within 30 days after antimicrobial therapy discontinuation (Liew et al., 2012).

The rates of clinical failure and 30-day re-infection assessed in patients having either one or both of the risk factors for thrombocytopenia were compared between the observational and intervention groups.

2.4. Statistical analyses

Data were analyzed using SPSS version 11 (SPSS Inc., Chicago, IL, USA). Parametric variables were analyzed using *t* test, while non-parametric variables were analyzed by the Mann–Whitney *U* test or χ^2 test or Fisher's exact probability test. Univariate and multivariate logistic regression analyses were performed to determine the odds ratios (ORs) and 95% confidence intervals (CIs) for thrombocytopenia. Variables that affect the incidence of thrombocytopenia with *P* value of less than 0.10 obtained from the observation study were subjected to the univariate as well as multivariate logistic regression analyses, in which clinically applicable threshold values for risk factors were determined by the receiver operating characteristic analysis. Moreover, several investigators reported that renal insufficiency (Lin et al., 2006) and prolonged treatment duration (Birmingham et al., 2003) are significant risk factors for linezolid-induced thrombocytopenia. Thus, these variables were also included in the logistic regression analyses. Kaplan–Meier plots for the development of linezolid-induced thrombocytopenia were obtained from patients having 1 or 2 of risk factors both in the observational and intervention studies, and the curves were statistically compared by log-rank Mantel-Cox analysis. *P* value of <0.05 was considered statistically significant. The power calculation was performed using IBM SPSS Sample Power 3 (Release 3.0.1) for evaluation of dose adjustment on the incidence of thrombocytopenia.

3. Results

3.1. Risk factors of linezolid-induced thrombocytopenia

Fifty patients (32 men and 18 women; median [range] age, 63 [33–85] years) were the subject of the observational study. Thrombocytopenia occurred in 9 (18%) who received linezolid injection. The median duration of therapy until development of thrombocytopenia was 10 days (range, 3–29 days), while median onset of nadir was 15 days (range, 3–40 days). The demographics of patients with and without linezolid-associated thrombocytopenia were shown in Table 1. Significant differences in daily dose (mg/kg) ($P = 0.009$) and body weight ($P < 0.001$) were found between patients with and without thrombocytopenia.

Table 1
Comparison of demographics of patients with and without linezolid-induced thrombocytopenia before introduction of pharmaceutical intervention.

	Without thrombocytopenia ($n = 41$)	With thrombocytopenia ($n = 9$)	*P* value
Gender (male/female), *n*	27/14	5/4	0.705[a]
Age (years), median (range)	62 (33–85)	66 (33–77)	0.798[b]
Height (cm)	162.9 ± 9.3	162.0 ± 9.1	0.790[c]
Body weight (kg)	61.3 ± 12.2	49.7 ± 4.4	<0.001[c]
Daily dose (mg/kg)	20.4 ± 4.2	24.3 ± 2.1	0.009[c]
Serum albumin (g/dL)	2.79 ± 0.65	2.66 ± 0.60	0.580[c]
Aspartate aminotransferase (IU/L)	32.1 ± 29.0	79.3 ± 85.0	0.137[c]
Alanine aminotransferase (IU/L)	42.3 ± 52.9	52.1 ± 41.3	0.604[c]
White blood cells ($/mm^3$)	12810 ± 10715	11201 ± 11785	0.690[c]
Platelets ($10^3/mm^3$)	274 ± 143	179 ± 96	0.064[c]
Treatment duration (days), median (range)	13 (3–48)	10 (3–46)	0.862[b]
Creatinine clearance (mL/min)	103.6 ± 89.0	64.5 ± 60.4	0.218[c]
Hemodialysis (with/without)	8/33	2/7	1.000[a]

Data are mean ± SD unless otherwise specified.
[a] Fisher's exact probability test.
[b] Mann–Whitney *U* test.
[c] *t* test.