Research Paper

Mechanism Underlying Linezolid-induced Thrombocytopenia in a Chronic Kidney Failure Mouse Model

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Abstract

Objective: To investigate the relationship between renal function and linezolid (LZD)-induced thrombocytopenia and elucidate the underlying mechanism using a chronic renal disease (CRD) mouse model. **Materials and Methods:** CRD was induced in 5-week-old male Institute of Cancer Research (ICR) mice by 5/6 nephrectomy. After this procedure, LZD (25 and 100 mg/kg) was administered intraperitoneally once every day for 28 days. Platelet counts, white blood cell (WBC) counts, and hematocrit (HCT) levels were measured every 7 days. 2-^{14}C-thymidine (0.185 MBq) was administrated intravenously to LZD-administered mice to evaluate the thymidine uptake ability of bone marrow. **Results:** Platelet counts were significantly lower in the LZD-administered CRD group than in the LZD-nonadministered groups at 14, 21, and 28 days ($P < 0.05$); however, these changes were not observed in LZD-administered mice with normal renal function, regardless of the duration of LZD administration. No significant changes were observed in WBC counts or HCT levels in any LZD-administered CRD mouse. Moreover, radioactive levels in bone marrow were not significantly different in each group. **Conclusions:** These results indicate that LZD-induced decreases in platelet counts were enhanced by renal impairment *in vivo*, suggesting that LZD-induced thrombocytopenia is not caused by nonimmune-mediated bone marrow suppression.

Keywords: Chronic renal disease model mouse, DNA synthesis ability, hematological effect, linezolid, thrombocytopenia

Introduction

Linezolid (LZD) is a member of the oxazolidinone class of synthetic antimicrobial agent against the Gram-positive bacteria responsible for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus.[1] LZD utilizes a novel mechanism of antibiotic activity; it has the ability to bind to the bacterial 50S ribosomal subunit and inhibit the formation of the 70S functional initiation complex and ultimately, protein synthesis, thereby exerting its antibiotic effects.[2] Since LZD is taken into the body and metabolized nonenzymatically, neither liver metabolism nor renal excretion affects its metabolism.[3] Therefore, dosage adjustments and intervals are not important regardless of the degree of liver damage, renal function, or severity of infectious diseases.[3] A previous study reported that LZD has serious side effects including LZD concentration-dependent thrombocytopenia and anemia.[4] LZD-induced thrombocytopenia has recently been associated with renal impairment. Furthermore, the risk of thrombocytopenia in patients with renal impairment was found to be increased by elevations in the trough concentration of LZD and area under the concentration curve.[4-9] Pea *et al*. reported that therapeutic drug monitoring is useful in LZD therapy.[8] The incidence of thrombocytopenia has become a major issue in patients with renal impairment who are being treated with LZD because it is higher than in patients with

Access this article online

Quick Response Code:

Website: www.jpharmacol.com

DOI: 10.4103/jpp.JPP_167_16

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How to cite this article: Nishijo N, Tsuji Y, Matsunaga K, Kutsukake M, Okazaki F, Fukumori S, *et al*. Mechanism underlying linezolid-induced thrombocytopenia in a chronic kidney failure mouse model. J Pharmacol Pharmacother 2017;8:8-13.

Received: 27-10-2016 **Revised:** 29-12-2016 **Accepted:** 27-01-2017

normal renal function (NRF), and thrombocytopenia results in the interruption of treatments with LZD.[9-16] However, the mechanism underlying LZD-induced thrombocytopenia has not yet been elucidated. Gerson *et al.* demonstrated that reductions in platelet counts were caused by the toxicity-induced suppression of platelet production by bone marrow and hematopoietic cells.[17] On the other hand, Bernstein *et al.* showed that LZD-induced thrombocytopenia was not caused by bone marrow suppression, but by the direct destruction of platelets by an immune reaction with a specific antibody.[18] However, these findings were obtained from clinical specimens, and other factors causing thrombocytopenia (e.g., concomitant drugs causing thrombocytopenia other than LZD, severity of underlying diseases, and platelet counts before the administration of LZD) were not excluded. In addition, a basic study on the mechanism responsible for thrombocytopenia has not yet been performed in an *in vivo* model.

Therefore, we herein clarified the relationship between renal function, reductions in platelet counts, and the mechanism underlying LZD-induced thrombocytopenia using a chronic renal disease (CRD) mouse model.

Materials and Methods

Animals

Five-week-old male ICR mice were purchased from Japan SLC, Inc. (Shizuoka, Japan) and housed under standardized light-dark cycle conditions (lights on and off at 7:00 and 19:00, respectively) at a room temperature of 24°C ± 1°C and humidity of 50% ±10% with free access to food and water. All animal handling protocols and surgical procedures were reviewed and approved by the Animal Experiment Committee at University of Toyama (A2012PHA-45).

Establishment of the chronic renal disease model by 5/6 nephrectomy

After a 1-week acclimatization period, we measured blood urea nitrogen (BUN) levels in all mice as a renal function index using a 10 Plate Colorimetric Detection Kit (Arbor Assays, Ann Arbor, Michigan, United States). Thirty-six mice were treated separately and subsequently divided into a NRF group ($n = 18$) or CRD model group ($n = 18$), and renal impairment was induced by 5/6 nephrectomy as a model of CRD.[19] In the first surgery, two-thirds of the left kidney was removed by excising the upper pole and lower pole under pentobarbital anesthesia. In the second surgery, the right kidney was completely removed, and 5/6 nephrectomy was performed 1 week after the first surgery. Twenty-eight days after the second surgery, BUN levels in the CRD and NRF groups were measured again to evaluate renal function.[20]

Administration of linezolid to normal renal function and chronic renal disease groups

Mice were divided into two subgroups: NRF and CRD. These two groups were further divided into the following three subgroups ($n = 6$ per group): the NRF group: (A) control (administered solvent), (B) administered 25 mg/kg LZD, and (C) administered 100 mg/kg LZD and the CRD model group: (D) control (administered solvent), (E) administered 25 mg/kg LZD, and (F) administered 100 mg/kg LZD.

LZD was dissolved in 10% dimethyl sulfoxide containing 5% glucose solution. LZD at 25 mg/kg or 100 mg/kg was administered intraperitoneally to the NRF (B and C) and CRD (E and F) groups once every day for 28 days, with the first day of the administration of LZD being defined as day 1. LZD solvent solution was administered to the NRF (A) and CRD (D) control groups once every day for 28 days. On days 0, 7, 14, 21, and 28 of the LZD administration protocol, blood samples were collected from the tail vein.

Platelet counts, white blood cell counts, and hematocrit levels

To evaluate the toxicity of LZD, platelet counts were measured using the Brecher-Cronkite method with the hemocytometer bacteria A161 (Sunlead Glass Corporation, Saitama, Japan).[21,22] We measured white blood cell (WBC) counts and hematocrit (HCT) levels with a microcell counter model F-520 (Sysmex, Hyogo, Japan).

Measurement of DNA composition ability of myeloblasts

We added another group, (G) nontreated control mice, to this evaluation.

On day 28, we diluted 2-^{14}C-thymidine (0.185 MBq) in 0.2 ml of isotonic saline and administrated it at a dose of 0.2 ml to the CRD model control group (D), 25 mg/kg administered group (E), 100 mg/kg administered group (F), and nontreated control group (G). Mice were sacrificed 1 h after the tail vein injection of 2-^{14}C-thymidine and then rapidly frozen in dry ice and acetone. We removed the hind leg surgically from the hip joint using clippers and exposed the femur and tibia. Mice from which the hind legs were removed were embedded in carboxymethylcellulose gel. Twenty micrometer-thick serial sections were made through the sagittal plane of each mouse with the tape-sectioning method using a Cryo Polycut cryostat (Reichert-Jung, Nussloch, Germany) at −20°C. Sections on adhesive tape (Yu-Ki Ban, Nitto Medical Co., Ltd., Osaka, Japan) were desiccated and placed on a BAS-MS2040 imaging plate (Fujifilm Co., Ltd, Tokyo, Japan) for 1 day. Whole-body macroautoradiographs were processed digitally with an FLA7000 image analyzer (Fujifilm Co., Ltd).

Statistical analysis

Data were analyzed using SPSS software version 18 (IBM, Tokyo, Japan), and graphical analyses were performed by R (version 3.2.2). $P < 0.05$ was considered statistically significant. BUN levels in the NRF (A, B, and C) and CRD (D, E, and F) groups were analyzed using an unpaired *t*-test. Platelet counts, WBC counts, and HCT levels were analyzed by a one-way analysis of variance and Dunnett's test. We defined the number of mice on day 0 as $n = 18$ because we collected

blood samples before the administration of LZD before grouping. On the other hand, we defined the number of mice on days 7, 14, 21, and 28 as $n = 6$ because the administration of LZD had already started, namely, after grouping. Day 0 and the control were defined as the control group in Dunnett's test. Moreover, we calculated the correlation coefficient with WBC counts and LZD in the CRD group on day 28 using Pearson's product-moment correlation.

Results

Establishment of the chronic renal disease model by 5/6 nephrectomy

Mean (standard deviation [SD]) BUN levels were 22.1 (3.5) and 50.4 (12.6) mg/dl in the NRF (A, B, and C) and CRD (D, E, and F) groups, respectively, and were significantly higher in the CRD group ($P < 0.05$).

Platelet counts, white blood cell counts, and hematocrit levels

In the NRF (A, B, and C) group, platelet counts in the 100 mg/kg LZD administration group (C) were significantly lower than platelet counts on day 28 compared with day 0 [Figure 1].

Moreover, platelet counts were also significantly lower in the 25 mg/kg LZD administration group (B) on days 14 and 28, and in the 100 mg/kg LZD administration group (C) on days 28 than control ($P < 0.05$).

In the CRD (D, E, and F) group, platelet counts in the control group (D) were significantly lower than platelet counts on days 7, 14, and 28 compared with day 0. Platelet counts were also significantly lower in the 25 mg/kg LZD administration group (E) on days 14, 21, and 28, and in the 100 mg/kg LZD administration group (F) on days 7, 14, 21, and 28 than on day 0. On days 21 and 28, platelet counts were significantly lower in the 25 mg/kg LZD administration group (E) than in the control group (D). Similarly, platelet counts on days 21 and 28 were significantly lower in the 100 mg/kg LZD administration group (E) than in the control group (D) ($P < 0.05$) [Figure 1].

WBC counts in the CRD (D, E, and F) group were measured at the same time as platelet counts [Figure 2]. WBC counts did not change throughout the administration of LZD to CRD (D, E, and F) mice. Moreover, no significant difference was observed in WBC counts between the control group and 25 mg/kg (E) or 100 mg/kg (F) LZD administration group (D). We also investigated the relationship between WBC counts and LZD doses. No dose-dependent reductions were observed in WBC counts ($P = 0.062$, $R = -0.448$). HCT levels were also measured in the CRD (D, E, and F) group at the same time as platelet counts [Figure 2].

No significant changes were noted in HCT levels in any of the LZD-administered CRD (D, E, and F) mice from day 0. Moreover, no significant differences were observed in HCT

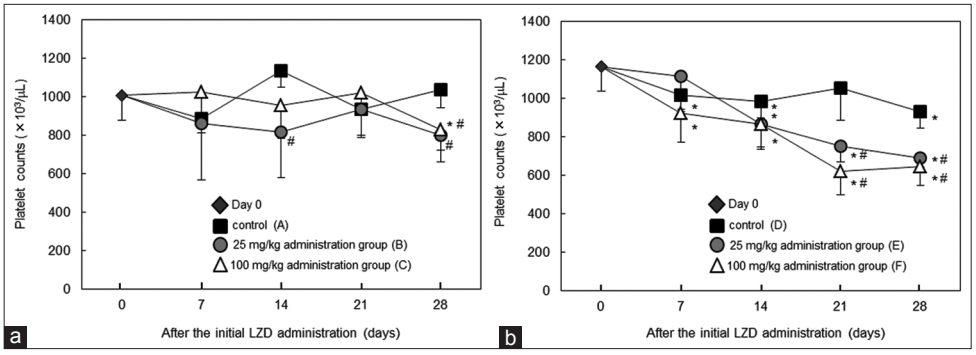

Figure 1: Platelet counts after the administration of linezolid to (a) normal renal function (A, B, and C) and (b) chronic renal disease (D, E, and F) groups. Day 0 is $n = 18$, and other symbols represent the mean ± standard deviation ($n = 6$)

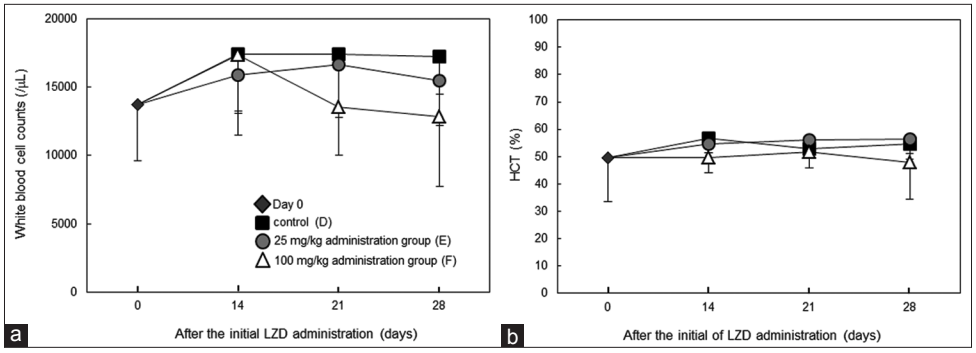

Figure 2: White blood cell counts and hematocrit levels after the administration of linezolid to the chronic renal disease (D, E, and F) group. (a) White blood cell counts and (b) hematocrit levels after the administration of linezolid to the chronic renal disease (D, E, and F) group

levels between the 25 mg/kg (E) or 100 mg/kg (F) LZD administration group and control group (D).

Measurement of DNA composition ability of myeloblasts

Figure 3 shows the results of whole-body macroautoradiograms taken 1 h after the administration of 2-^{14}C-thymidine. ^{14}C-radioactivity is indicated by color: regions in red, yellow, green, and blue show decreasing amounts in that order. Almost all radioactivities accumulated in bone marrow. However, radioactivity was not observed in other tissues in any of the mice examined. Radioactive levels in bone marrow were not significantly different between the (a) control group (D) and (b) CRD mice administered 100 mg/kg LZD (F).

Discussion

Previous case reports have been published on the mechanism underlying LZD-induced thrombocytopenia.[4-7,11-13,15,18] However, due to the nature of case reports, the mechanism responsible has not yet been elucidated in detail. We herein investigated the mechanism underlying the onset of LZD-induced thrombocytopenia as well as the relationship between renal impairment and LZD-induced thrombocytopenia using CRD (D, E, and F) mice, in which a number of factors may be excluded.

Significantly higher BUN levels were observed in mice subjected to 5/6 nephrectomy than in the NRF (A, B, and C) group. We subsequently performed experiments under these conditions to elucidate the mechanism underlying LZD-induced thrombocytopenia.

Platelet counts were significantly lower on days 14 and 28 than on day 0 in the CRD control group (D). A previous study reported that thrombocytopenia occurs in a drug-independent manner in patients with renal impairment.[23] A significant decrease in platelet counts from day 0 was observed after day 14 in the 25 mg/kg LZD administration group (E) and after day 7 in the 100 mg/kg LZD administration group (F). Furthermore, a significant difference was observed in platelet counts between the 25 mg/kg (E) and 100 mg/kg LZD administration groups (F) and control group (D). In contrast, in the NRF (A, B, and C) group, a significant difference was only observed on day 28 in the 100 mg/kg LZD administration group (C) compared with day 0 and day 14 and 28 in the 25 mg/kg LZD administration group (B) and day 28 in the 100 mg/kg LZD administration group (F) compared with control. Although a significant decrease in platelet counts in the NRF (A, B, and C) group, it was mild compared with CRD (D, E, and F) group. Therefore, the incidence of LZD-induced thrombocytopenia may be higher in a state of renal impairment than in NRF.

Loo *et al.* reported that two mechanisms were responsible for drug-induced thrombocytopenia:[24] nonimmune-mediated thrombocytopenia caused by the suppression of platelet production by bone marrow and immune-mediated thrombocytopenia caused by an immune reaction inducing the suppression of platelet production or acceleration of platelet destruction. Each mechanism is characteristic for the duration from the start of antimicrobial therapy to the occurrence of thrombocytopenia. The occurrence of nonimmune-mediated thrombocytopenia gradually increases from the start of antimicrobial therapy to 2–3 weeks after. On the other hand, the occurrence of immune-mediated thrombocytopenia has been reported from the start of antimicrobial therapy to 7–14 days after.[24] Gerson *et al.* found that nonimmune-mediated thrombocytopenia due to the suppression of bone marrow was related to the drug administration period and did not occur before days 10–14 from the start of antimicrobial therapy. Furthermore, immune-mediated thrombocytopenia was shown to occur earlier than nonimmune-mediated thrombocytopenia.[17] In the present study, platelet counts were significantly lower on day 7 than on day 0 in the CRD (D, E, and F) group, suggesting that the mechanism underlying LZD-induced thrombocytopenia was not caused by the suppression of platelet production by bone marrow.

Platelets are produced from the cytoplasm of megakaryocytes, which differentiate from hematopoietic stem cells.[25,26] If bone marrow suppression-induced nonimmune-mediated thrombocytopenia occurs, it suggests that decreasing hematopoietic stem cell-related pancytopenia is the cause of thrombocytopenia. On the other hand, platelet-specific reductions have been reported in immune-mediated thrombocytopenia induced by antiplatelet autoantibodies.[27] If LZD-induced

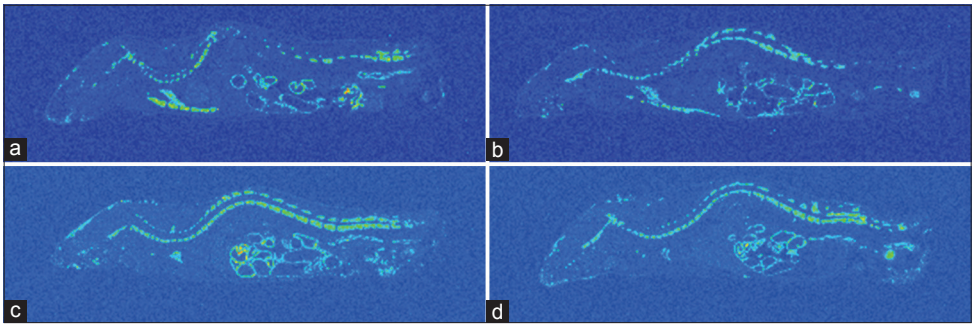

Figure 3: Whole-body autoradiography of chronic renal disease (a, b, and c) mouse and a nontreated control mouse (d). 2-^{14}C-thymidine was injected into the tail veins of a control chronic renal disease model mouse (a), a chronic renal disease model mouse that was administered 25 mg/kg linezolid for 28 days continuously (b), a chronic renal disease model mouse that was administered 100 mg/kg linezolid for 28 days continuously (c), and a nontreated control mouse (d) and the results of whole-body autoradiography 1 h later were shown

thrombocytopenia is caused by a nonimmune-mediated mechanism, it is expected to be accompanied by decreased WBC counts and HCT levels. The results of the present study indicated that WBC counts on day 28 in each group did not differ significantly. However, we suspect that dose-dependent decreases in WBC counts occurred. Therefore, we investigated the relationship between WBC counts and LZD doses. The results obtained showed the absence of dose-dependent reductions in WBC counts. Although platelet-specific reductions were observed in the present study, WBC counts and HCT levels did not significantly change from those on day 0 in the LZD-administered CRD (E and F) group, suggesting that the mechanism underlying LZD-induced thrombocytopenia was not caused by a decrease in platelet production by nonimmune-mediated bone marrow suppression.

Moreover, we added a complementary treatment for this result, an image analysis using whole-body macroautoradiography. The uptake of nucleic acid precursors is necessary for the synthesis of DNA.[28] Thymidine uptake ability increases in tissue, in which the synthesis of DNA is actively occurring. In the present study, the radioactivity was mostly found in bone marrow. Therefore, the synthesis of DNA appeared to be actively occurring in bone marrow. Thymidine uptake ability i.e., DNA synthesis ability of bone marrow was different in each group. However, thymidine uptake ability did not significantly differ between any of the groups examined, indicating that DNA synthesis ability was not altered by the administration of LZD to mice in each group. These results suggest that bone marrow inhibition is not the cause of LZD-induced thrombocytopenia and may be shown in an *in vivo* model.

This study has several limitations. We were unable to measure LZD blood concentrations for the identification of LZD-induced thrombocytopenia. Some clinical researchers have reported that LZD blood concentrations are higher in patients with renal impairment than in those with NRF and suggest that this increase is the cause of thrombocytopenia[4-6,9,29] Although we intended to measure LZD blood concentrations, the paucity of mouse blood samples prevented this. Another limitation is that we were unable to observe the differentiation process from hematopoietic stem cells to megakaryocytes or megakaryocytic differentiation, which is necessary for elucidating the mechanism underlying LZD-induced thrombocytopenia. However, based on blood analyses and whole-body macroautoradiography, we suggest that LZD-induced thrombocytopenia is caused by specific reductions in platelet counts and immune-mediated reactions.

Conclusions

LZD-induced thrombocytopenia was caused by impaired renal function from the NRF state *in vivo*. Based on measurements of WBC counts, HCT levels, and thymidine uptake ability, we demonstrated that LZD-induced thrombocytopenia was caused by specific reductions in platelet counts. Moreover, we revealed that the mechanism underlying LZD-induced thrombocytopenia did not involve nonimmune-mediated bone marrow suppression.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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