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ORIGINAL ARTICLE

A retrospective test for a possible relationship between linezolid-induced thrombocytopenia and hyponatraemia

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Abstract

What is known and objective: Thrombocytopenia is one of the typical adverse events caused by linezolid (LZD). Recently, some cases of severe hyponatraemia occurring while receiving LZD have been reported. This study investigated a possible relationship between LZD-induced hyponatraemia and thrombocytopenia and identified the risk factors for hyponatraemia and/or thrombocytopenia.

Methods: In this retrospective, single-centre, observational cohort study, 63 hospitalized patients aged over 18 years who received intravenous injection of LZD for more than seven consecutive days in Oita University Hospital between April 2015 and March 2018 were analysed.

Results: Thrombocytopenia occurred in 25 (39.7%) patients and hyponatraemia in 11 (17.5%) patients. Seven of 11 patients with hyponatraemia had concurrent thrombocytopenia. Although both serum sodium level and platelet count declined in most patients who developed hyponatraemia, no significant association between thrombocytopenia and hyponatraemia was found. Creatinine clearance level (Ccr) was significantly lower not only in the thrombocytopenia (vs no-thrombocytopenia) but also in the hyponatraemia group (vs no-hyponatraemia group). Univariate and multivariate logistic regression analyses identified different risk factors for thrombocytopenia and/or hyponatraemia (thrombocytopenia: Ccr and administration period; hyponatraemia: serum albumin; thrombocytopenia and hyponatraemia: administration period and serum albumin).

What is new and conclusion: In conclusion, this study found no significant relationship between LZD-induced thrombocytopenia and hyponatraemia and identified some possible risk factors associated with onset of the two adverse events. These require further validation.

KEYWORDS

hypoalbuminaemia, hyponatraemia, linezolid, thrombocytopenia

1 | WHAT IS KNOWN AND OBJECTIVE

Linezolid (LZD), an oxazolidinone antimicrobial agent, has potent activity for Gram-positive bacteria including multidrug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* (VRE).[1] The bioavailability of LZD is approximately 100%, and dose adjustment is not required even in patients with hepatic or renal dysfunction.[2,3] Moreover, the drug distributes abundantly in various tissues, particularly in epithelial lining fluid, spinal fluid and osseous tissue.[4-6] Because of these advantages, LZD is often used as empirical therapy for miscellaneous infections.

Thrombocytopenia is recognized to be the major adverse event induced by LZD, with a reported prevalence rate of about 15%-50%.[7-12] According to many previous reports, risk factors are suggested to be prolonged administration over 2 weeks,[7-9] higher dose per body weight,[9,10] renal dysfunction[7-12] and hypoalbuminaemia.[9] On the other hand, hyponatraemia also developed in 7% of the patients who received LZD therapy in a Japanese phase III clinical trial (Linezolid Japanese package). It is the most common dysfunction of electrolyte balance and body fluid encountered in the clinical setting and is defined as a condition of serum sodium (Na) level below 134 mEq/L. Hyponatraemia can cause a wide range of clinical symptoms, from minor symptoms such as headaches, nausea and anorexia to severe and even life-threatening conditions.[13] Thus far, four cases of severe hyponatraemia occurring while receiving LZD have been reported.[14-17]

Thrombocytopenia is a common adverse event of LZD, while the association of hyponatraemia with LZD is not well established. In a previous study, we retrospectively investigated the frequency and risk factors of LZD-induced hyponatraemia and identified plasma C-reactive protein (CRP) level before initiation of LZD and concomitant use of a potassium-sparing diuretic as the independent variables associated with the development of hyponatraemia.[18] Moreover, we have encountered several patients with hyponatraemia whose platelet (PLT) levels decreased concomitantly. Singhania et al[17] reported a case of concurrent hyponatraemia, bone marrow suppression and thrombocytopenia while receiving LZD. Many previous studies have suggested a relationship between LZD-induced thrombocytopenia and trough LZD concentration, and between trough concentration and creatinine clearance.[19-22] Although the association of trough LZD concentration with hyponatraemia has not been investigated, we speculated that thrombocytopenia and hyponatraemia may be related if the frequencies of the two adverse events increase due to elevated plasma LZD concentration. However, we found no reports focusing on thrombocytopenia and hyponatraemia during LZD administration, which compare the risk factors of and evaluate the relationship between these adverse effects.

In this study, we assessed a possible relationship between LZD-induced hyponatraemia and thrombocytopenia, and identified the risk factors of hyponatraemia and/or thrombocytopenia.

2 | METHODS

2.1 | Subjects

In this retrospective, single-centre, observational cohort study, medical records were reviewed to identify patients aged over 18 years who received intravenous injection of LZD for more than seven consecutive days in Oita University Hospital between April 2015 and March 2018. Exclusion criteria were as follows: PLT count below $100 \times 10^3/\mu L$ or Na level below 130.0 mEq/L prior to LZD initiation; admission to intensive care unit or emergency centre during LZD treatment; and no routine measurement of Na level or PLT count at least twice before and during LZD treatment. The retrospective study was started after approval by the Ethics Committee of Oita University Faculty of Medicine (Review reference number: 1420).

2.2 | Definition of hyponatraemia and thrombocytopenia

In a previous report, hyponatraemia was defined as Na level lower than 134 mEq/L after initiation of oxcarbazepine, an anti-epileptic drug.[23] However, there are some issues with this definition for the present study. While probably few patients with epilepsy have low baseline Na levels, more patients with infections presumably have low Na levels at baseline due to severe inflammation or electrolyte abnormality. Moreover, a slight change in Na level may also be classified as hyponatraemia. Therefore, the definition of hyponatraemia was modified as follows: Na level lower than 134 mEq/L and more than 5% decrease from baseline after initiation of LZD. Thrombocytopenia was defined as more than 30% decrease in PLT count compared to that before initiation of LZD, according to a previous report.[24] The definition of acute kidney injury was 0.5 mg/dL or more than 50% increase in serum creatinine level compared to that before initiation of LZD.[25]

2.3 | Data collection

Patient characteristics and laboratory data were collected from the electronic medical records. The extracted clinical data before LZD initiation were as follows: gender, age, body weight, dose per day, administration period, white blood cell (WBC) count, PLT count, CRP, serum albumin (ALB), serum creatinine and Na. PLT count, serum creatinine and Na were also followed after LZD initiation. Creatinine clearance (Ccr) was calculated by the Cockcroft-Gault Equation[26] Infectious diseases treated by LZD were assessed from medical consultation records.

2.4 | Statistical analysis

Statistical analyses were performed using Predictive Analytics Software (PASW) STATISTICS version 21 (SPSS Inc). Baseline clinical data

are expressed as number (%) for categorical variables and as median [interquartile range] for continuous variables. The relationship between thrombocytopenia and hyponatraemia was analysed by one-sided Fisher's exact test. For comparisons between two groups, data normality was tested using the Shapiro-Wilk test. Parametric data are expressed as mean ± standard deviation and non-parametric data as median [interquartile range]. Parametric data were analysed by Student's *t* test and non-parametric data by Mann-Whitney *U* test. The risk factors related to hyponatraemia and/or thrombocytopenia were analysed by univariate and multiple logistic regression, using the following as independent variables (data before LZD initiation): administration period, dose per body weight, age, PLT count, ALB, CRP, Na and Ccr. We selected the above factors as covariates in univariate analysis for the following reasons: administration period,[7-9] dose per body weight,[9,10] ALB[9] and Ccr[7-12] are known risk factor for LZD-induced thrombocytopenia; CRP is a known risk factor for hyponatraemia[18]; older people are more susceptible to develop hyponatraemia; PLT level is the parameter of thrombocytopenia (PLT); and Na level is the parameter of hyponatraemia. In common practice, variables with $P < .25$ in univariate analysis are included for analysis in multivariate models. When using this cut-off, however, many factors were incorporated into the multivariate analysis. Therefore, we set $P < .12$, which is less than half of 0.25, for inclusion into multivariate analysis. For multiple logistic regression analysis, independent variables were inserted stepwise in the model using Schwarz's Bayesian information criterion and the variable remained in the model if $P < .05$.

3 | RESULTS

3.1 | Patient characteristics

Sixty-three patients who satisfied the selection criteria were analysed. The demographic and laboratory data of the patients are shown in Table 1. The ratio of male to female was 36 to 27, and median age at the time of initiation of LZD treatment was 63.0 years. The median administration period was 12 days, and LZD was most frequently used for the treatment of post-operative incision infection, followed by arthritis, cellulitis and osteomyelitis. MRSA was detected in blood culture and/or infected lesion culture of 37 patients. Median PLT count before initiation of LZD was 273.0 × 10^3/μL, and median Na level was 138.0 mEq/L. Of 63 patients, 25 (39.7%) developed thrombocytopenia and 11 (17.5%) developed hyponatraemia after initiation of LZD.

TABLE 1 Demographic and clinical characteristics of patients

Characteristics	Value
Total patients; n	63
Hyponatraemia patients; n (%)	11 (17.5)
Thrombocytopenia; n (%)	25 (39.7)
Gender (male/female); n (%)	36 (57.1)/27 (42.9)
Age (y)	63.0 [54.0-79.5]
Body weight (kg)	57.8 [50.3-69.8]
Dose/body weight (mg/kg)	20.8 [17.0-23.6]
Administration period (d)	12 [9-14]
White blood cell (×10^3 cells/mm^3)	7.11 [5.27-10.47]
Platelet count (×10^3/μL)	273.0 [217.5-329.0]
C-reactive protein (mg/dL)	3.46 [0.91-9.57]
Albumin (g/dL)	3.13 [2.50-3.58]
Serum creatinine (mg/dL)	0.75 [0.57-1.19]
Creatinine clearance (mL/min)	69.6 [38.3-116.7]
Serum sodium (mEq/L)	138.0 [135.7-140.2]
Infection; n (%)	
Post-operative incision infection	17 (30.0)
Arthritis	7 (11.1)
Cellulitis	7 (11.1)
Osteomyelitis	7 (11.1)
Pyogenic spondylitis	6 (9.5)
Pneumonia	5 (7.9)
Cerebral abscess	3 (4.8)
Decubitus ulcer	2 (3.2)
Pyothorax	1 (1.6)
Cholecystitis	1 (1.6)
Urinary tract infection	1 (1.6)
Pulmonary suppuration	1 (1.6)
Unknown	5 (7.9)
Methicillin-resistant *Staphylococcus aureus* detection; n (%)	37 (58.7)

Note: Data are expressed as numbers (%) for categorical variables and median [interquartile range] for continuous variables.

3.2 | Relationship between LZD-induced hyponatraemia and thrombocytopenia

Seven of 11 patients with hyponatraemia had concurrent thrombocytopenia. The frequencies of hyponatraemia in thrombocytopenia and no-thrombocytopenia groups were 28.0% or 10.5%, respectively. The time to onset of adverse events after LZD initiation was 10.0 and 11.0 days for hyponatraemia and thrombocytopenia, respectively, with no significant difference (data not shown). Figures 1 and 2 show the changes of PLT count and Na level in four patients with hyponatraemia but no thrombocytopenia, and in seven patients with both hyponatraemia and thrombocytopenia, respectively. In all patients with concurrent hyponatraemia and thrombocytopenia, both Na level and PLT count decreased (Figure 2). The four patients with hyponatraemia but no thrombocytopenia did not meet the thrombocytopenia definition in our study, although their PLT counts also decreased, as did Na level (Figure 1). Of note, Na level recovered earlier after LZD discontinuation compared to PLT count. However, no significant association was found between the incidence of hyponatraemia in patients with and those without thrombocytopenia (Table 2).

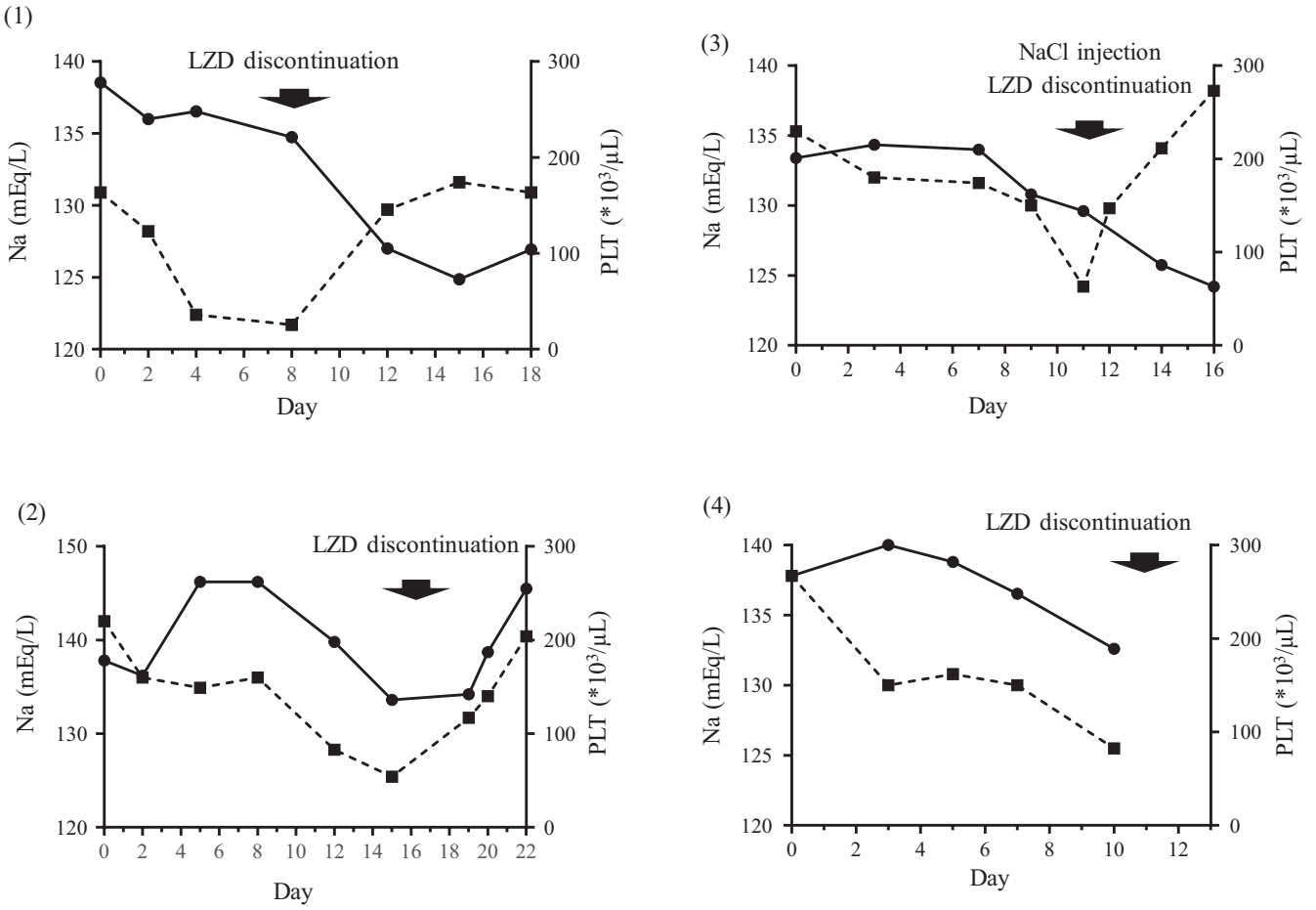

FIGURE 1 Changes of platelet count and serum sodium level over time in four patients with hyponatraemia without thrombocytopenia. Black circles and solid line represent platelet count. Black square and dotted line represent serum sodium level

3.3 | Comparison of Ccr for thrombocytopenia vs no thrombocytopenia and hyponatraemia vs no hyponatraemia

Renal impairment is a representative risk factor for thrombocytopenia while receiving LZD.[7-12] Comparison of Ccr levels in four groups showed that Ccr was significantly lower not only in the thrombocytopenia group (vs no-thrombocytopenia group) but also in the hyponatraemia group (vs no-hypothermia group; Figure 3). None of the patients with hyponatraemia developed acute kidney injury or were additionally prescribed diuretic drugs after LZD initiation. Thus, the possibility of reduction in blood Na level due to fluid overload or diuretic use was excluded.

3.4 | Identification of risk factors for thrombocytopenia or/and hyponatraemia by multivariate logistic regression

A univariate analysis to identify risk factors for the development of thrombocytopenia and/or hyponatraemia extracted the following variables ($P < .12$): administration period, age and Ccr for thrombocytopenia (Table 3); age, Ccr, dose/body weight, ALB and CRP for hyponatraemia (Table 4); and administration period, age, ALB and CRP for concurrent thrombocytopenia and hyponatraemia (Table 5). Multiple logistic regression analysis by a stepwise selection of the factors extracted by the univariate analysis identified Ccr and administration period as independent factors associated with development of thrombocytopenia (Table 3); ALB as independent factors for hyponatraemia (Table 4); and administration period and serum ALB as independent factors for concurrent thrombocytopenia and hyponatraemia (Table 5).

4 | DISCUSSION

In this retrospective study, we analysed the relationship between thrombocytopenia, a major adverse effect of LZD, and hyponatraemia that has recently been reported to develop during LZD treatment, and identified risk factors for both or either of these two adverse effects. The findings obtained in this study are as follows. (a) Fisher's exact test detected no statistically significant association between thrombocytopenia and hyponatraemia (Table 2), although both Na level and PLT count declined in most of the patients who developed

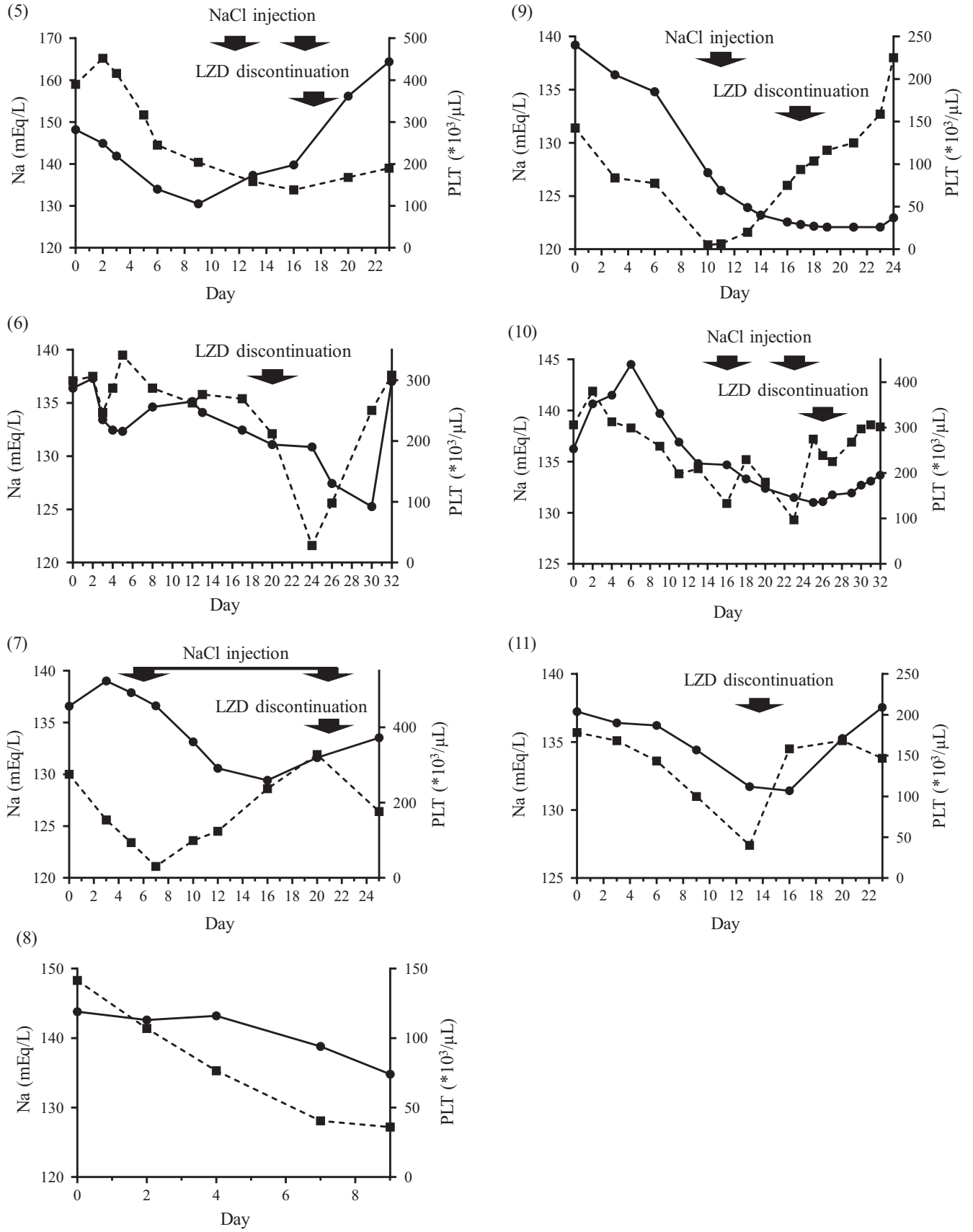

FIGURE 2 Changes of platelet count and serum sodium level in seven patients with both hyponatraemia and thrombocytopenia. Black circles and solid line represent platelet count. Black square and dotted line represent serum sodium level

TABLE 2 Relationship between linezolid-induced hyponatraemia and thrombocytopenia

	Hyponatraemia (+; n)	Hyponatraemia (−; n)	Rate of hyponatraemia (%)	*P* value
Thrombocytopenia (+)	7	18	28.0	.075
Thrombocytopenia (−)	4	34	10.5	

Note: Analysed by one-sided Fisher's exact test.
Abbreviation: n, number of patients.

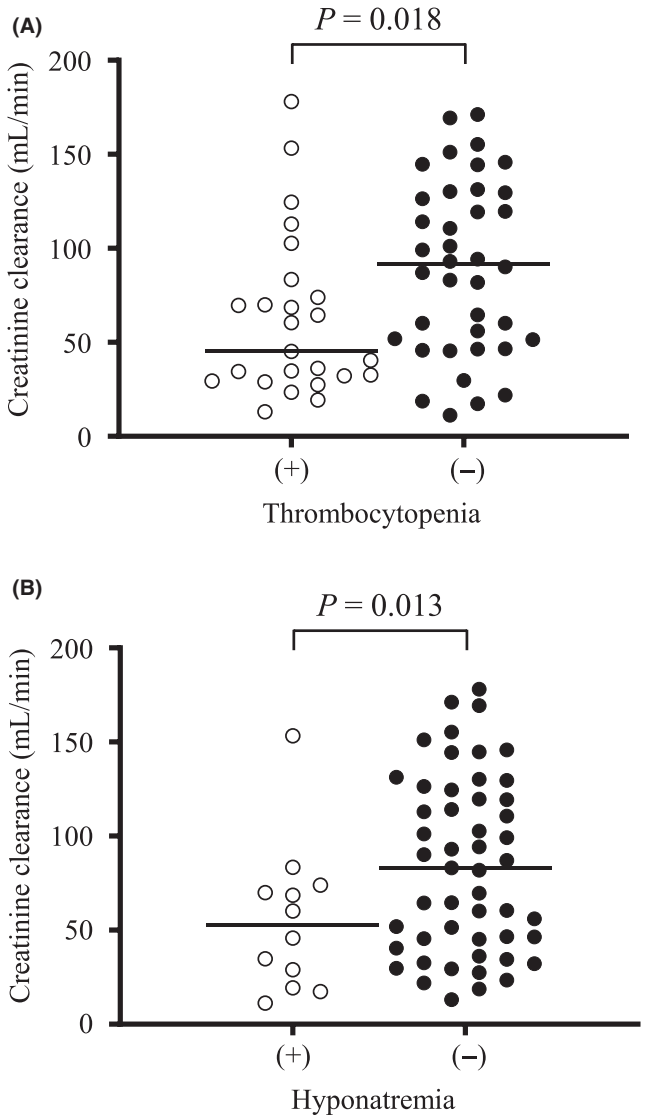

FIGURE 3 Comparison of creatinine clearance between thrombocytopenia and no-thrombocytopenia groups (A), and between hyponatraemia and no-hyponatraemia groups (B). Shapiro-Wilk test showed that the data were not normally distributed, and the non-parametric data were analysed by Mann-Whitney *U* test. Bar indicates median

hyponatraemia (Figures 1 and 2). (b) Ccr level known to be a representative risk factor of LZD-induced thrombocytopenia was lower in patients with thrombocytopenia or hyponatraemia compared to patients without these adverse events (Figure 3). (c) Univariate and multivariate logistic regression analyses showed that the risk factors associated with thrombocytopenia (Ccr and administration period) were different from those related to hyponatraemia (ALB) or concurrent thrombocytopenia and hyponatraemia (administration period and ALB; Tables 3-5).

The frequency of thrombocytopenia development after LZD initiation was 41% in this study. A search of the literature found that the reported frequencies varied from 15% to 50%.[7-12] According to the report of Takahashi et al[24] who used the same definition of thrombocytopenia as ours, the frequency was 38.7%, which is similar to our finding. However, their study included patients taking oral LZD and patients who received short treatment of less than 1 week. Since administration for longer than 10 days was found to be a risk factor of LZD-induced thrombocytopenia,[7-9] the frequency of thrombocytopenia was expected to be higher in our study compared to that of Takahashi et al[24] The reason why our rate was not higher is probably due to more active monitoring and intervention in patients administered LZD by the antimicrobial stewardship team in the era of our study (2015 to 2018) compared to the that of Takahashi et al[24] (2007 to 2009). Consequently, close monitoring of PLT count and early switch to other agents when PLT count starts to decrease may have been done more frequently for patients in our study. On the other hand, the incidence of LZD-induced hyponatraemia was 17.5%, which is almost the same as that in our previous research.[18] By excluding patients receiving treatment for less than one week, the incidence was expected to increase, but this was not observed. This is probably due to our modification of the definition of hyponatraemia to include 5% or more reduction of Na level from baseline level in addition to a decrease to below 134 mEq/L. This could have excluded some of the transient decreases caused by the infection itself or other factors early in treatment.

As shown in Figure 2, similar transitions between PLT count and Na level were observed in patients with concurrent thrombocytopenia and hyponatraemia. Furthermore, a similar transition was observed in patients with hyponatraemia but no thrombocytopenia, although the reduction in PLT count from baseline did not reach lower than 30% (Figure 1). In two of these four patients, PLT count continued to decrease even after LZD was discontinued and fulfilled the criterion of thrombocytopenia several days after discontinuation. However, Fisher's exact test failed to prove a significant relationship between the occurrence of thrombocytopenia and hyponatraemia (Table 2). Meanwhile, hyponatraemia improved earlier by sodium chloride injection and/or withdrawal of LZD, while PLT counts continued to decline for some time even after drug withdrawal. The different transition patterns would be useful information when monitoring these adverse events.

According to multivariate logistic regression analysis in Table 3, Ccr and administration period were extracted as independent variables for thrombocytopenia. Almost all the previous reports on

TABLE 3 Univariate (upper table) and multivariate analyses (lower table) for factors associated with linezolid-induced thrombocytopenia

Univariate analysis			
Covariate	**Thrombocytopenia**	**No-thrombocytopenia**	***P* value**
Administration period (d)	14.0 [10.0-15.0]	11.0 [8.0-14.0]	.110[a]
Dose/body weight (mg/kg)	19.9 ± 5.8	21.0 ± 4.7	.407[b]
Age (y)	73.0 [57.0-83.0]	62.0 [51.0-76.25]	.071[a]
Platelet count ($\times 10^3/\mu L$)	277.4 ± 94.2	287.9 ± 101.1	.681[b]
Serum albumin (g/dL)	3.05 ± 0.77	3.15 ± 0.71	.616[b]
C-reactive protein (mg/dL)	6.19 [1.62-12.00]	2.98 [0.72-6.54]	.156[a]
Serum sodium (mEq/L)	136.9 [135.2-138.6]	138.9 [136.9-140.2]	.127[a]
Creatinine clearance (mL/min)	45.2 [32.2-74.0]	91.6 [51.5-128.8]	.018[a]

Multivariate analysis					
				Odds ratio	
Dependent variable	**Independent variable**	**SE (%)**	***P* value**	**Estimate**	**95% CI**
Thrombocytopenia	Creatinine clearance	0.007	.018	0.985	0.972-0.997
	Administration period	0.080	.046	1.173	1.003-1.373

Note: Univariate analysis: Data normality was analysed by Shapiro-Wilk test. Non-parametric data are expressed as median [interquartile range] and parametric data as mean ± standard deviation.

Multivariate analysis: Variables with $P < .12$ in univariate analysis were entered in multivariate models. Independent variables were inserted stepwise using Schwarz's Bayesian information criterion (BIC) and remained in the model if $P < .05$.

Abbreviations: SE, standard error; 95% CI, 95% confidence interval.

[a] Mann-Whitney *U* test.

[b] Student's *t* test.

LZD-induced thrombocytopenia identified Ccr as a significant covariate. LZD is recognized as an anti-MRSA drug that does not require dose adjustment in patients with impaired renal function. However, the urinary extraction rate of unchanged drug is approximately 30%; therefore, plasma concentration increases in patients with end-stage renal failure and patients receiving dialysis. Some previous studies of population pharmacokinetic analysis demonstrated that Ccr was as a covariate of clearance and that trough concentration increased as renal function decreased.[19-22] Since plasma trough concentration correlates with the incidence of thrombocytopenia, elevation of trough concentration due to reduced renal clearance has been suggested to cause an increase in frequency of thrombocytopenia.[19,22]

On the other hand, ALB level but not Ccr was identified as an independent variable affecting the development of hyponatraemia, suggesting that the risk of hyponatraemia increases when ALB level is low (Table 4). Four cases of hyponatraemia while receiving LZD therapy have been reported.[14-17] In two of the four cases, a contributing factor for hyponatremia has signalled strongly a syndrome of inappropriate antidiuretic hormone secretion (SIADH).[15,16] SIADH is a condition of unsuppressed antidiuretic hormone (ADH) secretion from the posterior pituitary gland despite reduced serum osmotic pressure, followed by hypotonia due to relative ADH excess and persistent hyponatraemia.[27] SIADH is the main cause of euvolemic hyponatraemia and is often associated with underlying diseases in central nervous system or stimulation of ADH secretory pathway in the brain by medications such as antidepressants, anti-epileptics and antipsychotic agents. LZD has the characteristics of high distribution in the central nervous system (CNS). In common, only free drugs (unbound to serum protein) migrate to the CNS. Therefore, an increase in free drug fraction associated with hypoalbuminaemia may cause an increase in frequency of hyponatraemia due to SIADH. However, LZD has a low protein binding rate of approximately 20%-30%,[28] suggesting little effect of increased free drug fraction. In general, oncotic pressure decreases in hypoalbuminaemia, causing reduced effective plasma volume in blood vessel. Pressoreceptors sense the decreased pressure and activate the renin-angiotensin-aldosterone and ADH secretion system as compensatory response, allowing reabsorption of sodium and water by kidney tubule. The mean ALB level before LZD initiation was significantly lower in the hyponatraemia group than in the no-hyponatraemia group (2.38 ± 0.52 vs 3.26 ± 0.67 g/dL, $P < .001$; Table 4). Taken the above information into consideration, we speculate that LZD stimulates the central ADH secretory pathway under a condition of elevated ADH level due to hypoalbuminaemia and induces the development of hyponatraemia. However, we did not measure plasma ADH and osmolality level for assessment of SIADH, which is a limitation of this research.

As shown in Table 5, ALB level and administration period were identified as risk factors for concurrent thrombocytopenia and hyponatraemia. Regarding ALB level, both *P* value and odds ratio for concurrent thrombocytopenia and hyponatraemia were inferior compared to the analysis of hyponatraemia alone. Therefore, it would be more appropriate to consider hypoalbuminaemia as a risk factor for hyponatraemia alone. On the other hand, the odds ratio of administration period was 1.173 for thrombocytopenia alone and

TABLE 4 Univariate (upper table) and multivariate analyses (lower table) for factors associated with linezolid-induced hyponatraemia

Univariate analysis			
Covariate	**Hyponatraemia**	**No-hyponatraemia**	***P* value**
Administration period (d)	14.0 [10.5-15.5]	7.32 [4.18-11.50]	.161[a]
Dose/body weight (mg/kg)	22.9 ± 5.1	20.1 ± 5.1	.109[b]
Age (y)	76.5 ± 11.2	60.8 ± 18.4	.009[b]
Platelet count (×10^3/μL)	251.4 ± 85.4	290.6 ± 99.6	.230[b]
Serum albumin (g/dL)	2.38 ± 0.52	3.26 ± 0.67	<.001[b]
C-reactive protein (mg/dL)	7.32 [4.18-11.50]	2.92 [0.62-7.73]	.020[a]
Serum sodium (mEq/L)	138.7 ± 8.5	138.0 ± 3.5	.780[b]
Creatinine clearance (mL/min)	45.8 [24.1-69.3]	85.1 [45.4-124.9]	.013[a]

Multivariate analysis					
				Odds ratio	
Dependent variable	**Independent variable**	**SE (%)**	***P* value**	**Estimate**	**95% CI**
Hyponatraemia	Serum albumin	0.772	.001	0.086	0.019-0.391

Note: Univariate analysis: Data normality was analysed by Shapiro-Wilk test. Non-parametric data are expressed as median [interquartile range] and parametric data as mean ± standard deviation.

Multivariate analysis: Variables with $P < .12$ in univariate analysis were entered in multivariate models. Independent variables were inserted stepwise using Schwarz's Bayesian information criterion (BIC) and remained in the model if $P < .05$.

Abbreviations: SE, standard error; 95% CI, 95% confidence interval.

[a]Mann-Whitney *U* test.

[b]Student's *t* test.

TABLE 5 Univariate (upper table) and multivariate analyses (lower table) for factors associated with linezolid-induced thrombocytopenia + hyponatraemia

Univariate analysis			
Covariate	**Thrombocytopenia + hyponatraemia**	**No-thrombocytopenia + hyponatraemia**	***P* value**
Administration period (d)	14.0 [13.5-19.5]	11.0 [8.75-14.0]	.048[a]
Dose/body weight (mg/kg)	22.5 ± 5.2	20.3 ± 5.2	.306[b]
Age (y)	76.9 ± 10.4	61.9 ± 18.4	.041[b]
Platelet count (×10^3/μL)	263.0 ± 102.5	286.3 ± 97.8	.556[b]
Serum albumin (g/dL)	2.5 ± 0.6	3.2 ± 0.7	.015[b]
C-reactive protein (mg/dL)	10.02 [4.61-11.50]	3.03 [0.67-7.73]	.069[a]
Serum sodium (mEq/L)	140.0 ± 10.3	137.9 ± 3.6	.604[b]
Creatinine clearance (mL/min)	68.6 [31.9-72.0]	75.7 [44.0-120.8]	.189[a]

Multivariate analysis					
				Odds ratio	
Dependent variable	**Independent variable**	**SE (%)**	***P* value**	**Estimate**	**95% CI**
Thrombocytopenia and hyponatraemia	Administration period	0.140	.021	1.382	1.050-1.817
	Serum albumin	0.968	.037	0.132	0.020-0.883

Note: Univariate analysis: Data normality was analysed by Shapiro-Wilk test. Non-parametric data are expressed as median [interquartile range] and parametric data as mean ± standard deviation.

Multivariate analysis: Variables with $P < .12$ in univariate analysis were entered in multivariate models. Independent variables were inserted stepwise using Schwarz's Bayesian information criterion (BIC) and remained in the model if $P < .05$.

Abbreviations: SE, standard error; 95% CI, 95% confidence interval.

[a]Mann-Whitney *U* test.

[b]Student's *t* test.

1.382 for concurrent thrombocytopenia and hyponatraemia, and was higher for the latter. This suggests that prolonged administration increases the risk of not only thrombocytopenia but also concurrent hyponatraemia. Thus, not only PLT count but also Na level should be monitored in prolonged use of LZD.

5 | WHAT IS NEW AND CONCLUSION

To our best of knowledge, this retrospective research is the first report on the relationship between LZD-induced thrombocytopenia and hyponatraemia, although there is a limitation of small sample size of only 63 patients. In conclusion, there is no significant relationship between the two adverse events: thrombocytopenia and hyponatraemia, and the changes after discontinuation of LZD as well as the risk factors associated with the two adverse events are possible to be different. Na level should be monitored closely when ALB is low, and PLT count has to be monitored closely in patients with renal impairment or on prolonged treatment. Prompt measures such as drug withdrawal, sodium chloride injection and transfusion should be taken when Na level and PLT count decrease. However, these require further validation.

CONFLICT OF INTEREST

None.

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