Title

Investigation of the Risk Factors of Vomiting during Linezolid Therapy: A Retrospective Observational Study

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Abstract

Purpose Some clinical studies have reported the occurrence of nausea and vomiting with linezolid (LZD) administration. However, no studies have evaluated nausea and vomiting as primary endpoints. In a previous study, we noted a possible relationship between LZD and vomiting, but risk factors were not identified. Therefore, the aim of the present study was to identify them.

Methods Patients who received LZD 600 mg twice daily at Hokkaido University Hospital from September 2008 to April 2019 were enrolled in this retrospective observational study. Patient characteristics, concomitant medications, laboratory data, and the occurrence of vomiting were obtained from electronic medical records. Logistic regression analysis was performed to identify risk factors for vomiting, including age, sex, body weight, concomitant medications, and surgeries.

Results A total of 496 patients were included in this study, of which 90 experienced vomiting. By multivariate logistic regression analysis, female sex (adjusted odds ratio [aOR], 2.69; 95% confidence interval [CI], 1.62–4.47), ≥10 days of LZD administration (aOR, 2.57; CI, 1.46–4.50), and hyponatremia (aOR, 2.96; CI, 1.72–5.10) were identified as independent risk factors for vomiting; administration of serotonergic agents (aOR, 0.23; CI, 0.07–0.82) was negatively associated.

Conclusions This study is the first to successfully identify risk factors for LZD-induced vomiting. Careful monitoring of patients with these risk factors may lead to safer and sustainable LZD administration.

Introduction

Linezolid (LZD) is an antimicrobial agent used against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci. It is widely used to treat bacteraemia, pneumonia, and skin and soft tissue infections [1–2]. It has also been used to treat bone and joint infections [1] because it penetrates bone and joints well [3]. Previously, we observed multiple cases of nausea and vomiting, during LZD treatment for bone and joint infections. In a meta-analysis of phase III studies of LZD [4], the incidence of LZD-related vomiting was 1.1%. Another phase III study that compared the efficacy of LZD with tedizolid reported a nausea incidence of 12.2% and vomiting incidence 5.6% in patients receiving LZD [5]. The other meta-analysis focused on the efficacy and safety of LZD relative to other antibiotics and reported a nausea risk ratio of 1.58 (95% confidence interval [CI]: 0.91–2.74) and a vomiting risk ratio of 1.70 (95% CI: 1.02–2.82) [6]. In these studies, the LZD dose was 1,200 mg daily administered for approximately 10 days [4–6]. The incidence of LZD-related gastrointestinal adverse reactions, including nausea and vomiting, was 48.5%, occurring between 2 and 4 weeks of LZD treatment for drug-

resistant tuberculosis (XDR-TB) infection; the dose was 1,200 mg daily during the first 4–6 weeks and then 300–600 mg daily as tolerated, administered for 2–24 months [7]. Therefore, nausea and vomiting may be more common with LZD than with other antibiotics. However, these reports on nausea and vomiting were evaluated as part of the efficacy and safety of linezolid. To date, only our previous study has evaluated the incidence and/or risk factors for LZD-induced nausea and vomiting as the primary endpoint [8]. Although dose adjustments are not needed for renal function or body weight, plasma LZD concentration has been reported to increase in patients with renal impairment and those who are underweight, leading to thrombocytopenia [9–10]. In addition, LZD interacts with selective serotonin reuptake inhibitors (SSRIs) due to its non-selective monoamine oxidase (MAO) inhibitory activity [11], which may cause serotonin (5-hydroxytryptamine; 5-HT) syndrome [12].

In clinical settings, given patient variations and concomitant medications, it is possible that alterations in LZD pharmacokinetics and/or drug-drug interactions may induce nausea and vomiting. In a previous study, we reported that patients receiving LZD had a significantly higher incidence of vomiting than patients treated with other antibiotics; however, we could not investigate the risk factors for LZD-induced vomiting because of the insufficient number of patients enrolled [8]. Therefore, this study aimed to identify the risk factors associated with LZD-induced vomiting.

Materials and Methods

Study design

A single-centre, retrospective, observational study was conducted.

Population and sample size

The inclusion criterion for this study was treatment with LZD, 600 mg twice daily, orally or intravenously for the first time at Hokkaido University Hospital from September 2008 to April 2019. The exclusion criteria were: age <18 years, <3 days of administration, at least one vomiting episode within 1 week before the start of LZD administration, and missing data. Patients who met the criteria were divided into vomiting and non-vomiting groups. The intended sample size was 500 cases for the logistic regression analysis. In this regression model, it has been reported that when events per variate (EPV) ≥10, there were no major problems with the accuracy and precision of the results, but when EPV <10, the bias of the regression coefficients increased and often led to extreme values of the maximum likelihood estimates [13]. Thus, our calculated sample size was needed to incorporate 10 independent variables if the incidence of vomiting was assumed to be 20%, based on a previous study [8].

Data collection

The following information was extracted from medical records retrospectively: occurrence of vomiting, sex, age, body weight, serum creatinine level, baseline and minimum serum sodium level (S-Na) during the administration period, administration period of LZD, administration route, concomitant medications, surgery under general anaesthesia, and cancer chemotherapy. Dopamine type2 (D2) receptor blockers, serotonergic agents, opioid analgesics, tramadol, and rifampicin (RFP) were extracted as concomitant medications. Creatinine clearance (Ccr) was calculated using the Cockcroft-Gault formula [14]. Onset of vomiting was defined as the reflux of gastric contents from the mouth. Information about S-Na was extracted because antidiuretic hormone inappropriate secretion syndrome, which is a rare side effect of LZD, may occur, and nausea is a symptom of hyponatremia [15].

With regard to concomitant drugs, treatment with tramadol and other opioids was extracted separately because tramadol is a weak MAO inhibitor and its interaction with LZD was considered. To investigate whether D2 receptor blockers contribute to the suppression of vomiting, patients were scored for treatment with D2 receptor blockers at the start of LZD administration. Serotonergic agents were defined as drugs that stimulate or enhance the effects of 5-HT receptors and did not include antagonists. Since RFP interacts with LZD [16], it was also evaluated.

Considering postoperative nausea and vomiting (PONV) [17], patients who received LZD within 3 days after surgery under general anaesthesia were defined as "patients with operation." Similarly, considering the incidence of chemotherapy-induced nausea and vomiting (CINV) [18], patients who received LZD within 7 days after cancer chemotherapy were defined as "patients with cancer chemotherapy."

Definitions and measurements

The primary endpoint was the identification of risk factors for vomiting associated with LZD administration. Time from the start of LZD administration to the onset of vomiting was also evaluated. Risk factors for vomiting were defined separately as direct or potential. Direct factors that may be directly related to vomiting were: hyponatremia (S-Na ≤134 mEq/L) [19], use of concomitant drugs (D2 receptor blockers, serotonergic agents, opioid analgesics, tramadol, RFP), operation, and cancer chemotherapy. The potential risk factors were: elderly (≥65 years of age), female sex, low body weight (<40 kg), route of administration (intravenous infusion), duration of administration (≥10 days), renal impairment (Ccr <60 mL/min), and renal replacement therapy. Female sex was evaluated because this factor has been reported as a risk factor for nausea and vomiting in PONV and CINV [17–18]. Since low body weight and renal impairment generally increase LZD concentration, they have also been evaluated as risk factors [9–10]. The cut-off value for the administration period was determined using an ROC curve. Hyponatremia was defined as S-Na >134 mEq/L and ≤134 mEq/L before the start of and after LZD administration, respectively [19]. Because there are several reports on LZD-induced hyponatremia [20–21], we examined the incidence of vomiting in patients with or without hyponatremia to evaluate its contribution. Hyponatremia was stratified according to the Common Terminology Criteria for Adverse Events v5.0 [22] because it was necessary to distinguish between patients whose hyponatremia developed before and after LZD administration.

Data analysis

Statistical analyses were performed using JMP® 14 (SAS Institute Inc., Cary, NC, USA). To compare patient characteristics, the Mann-Whitney U test was performed for continuous variables, with Pearson's chi-squared test or Fisher's exact test performed for categorical variables. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) using logistic regression analysis were evaluated to identify risk factors. Statistical significance was set at P <0.05. Direct risk factors were inevitably incorporated into multivariate analysis: hyponatremia, concomitant use of dopamine D2 blockers, serotonergic agents, opioids, tramadol, RFP, operations, and cancer chemotherapy. For other potential risk factors (elderly, sex, low body weight, route of administration, duration of administration, renal impairment, and renal replacement therapy), we performed multivariate analysis for only those that were P <0.2 in univariate analysis.

Results

Patient characteristics

LZD was administered to 724 patients, of whom 496 satisfied the inclusion criteria (Fig. 1). Ninety patients who developed vomiting were allocated to the vomiting group, with the remaining 406 in the non-vomiting group. The incidence of vomiting was 18.1%. The median time from the start of LZD administration to the first onset of vomiting was 6 days (range 1–33). Significant differences between the vomiting and non-vomiting groups were observed for female sex (44.4% vs. 33.5%), body weight [median, 55.4 kg (range 35.9–110.0) vs. 60.0 kg (range 32.4–118.1)], administration period [median 14 days (range 4–64) vs. 10 days (range 4–41)], S-Na at baseline [median 138 mEq/L (range 128–151) vs. 139 mEq/L (range 116–182)], minimum S-Na during the administration period [median, 133.5 mEq/L (range 116–146) vs. 136 mEq/L (range 116–172)], hyponatremia (40.0% vs. 17.2%) including each grade classification, and concomitant use of RFP (14.4% vs. 6.4%) (Table 1).

Logistic regression analysis

Female sex, administration period, and renal impairment were P <0.2 in univariate analysis and therefore incorporated into the multivariate analysis with direct risk factors. In the multivariate logistic regression analysis, female sex (aOR, 2.69; 95% CI, 1.62–4.47), administration period (≥10 days) (aOR, 2.57; CI, 1.46–4.50), hyponatremia (aOR, 2.96; CI, 1.72–5.10), and concomitant use of serotonergic agents (aOR, 0.23; CI, 0.07–0.82) were identified as risk factors for vomiting (Table 2).

Vomiting in patients with or without hyponatremia

The incidence of vomiting in patients with hyponatremia was approximately twice as high as that in patients without hyponatremia (26.7% vs. 12.2%). In particular, the incidence of vomiting was higher in patients with hyponatremia that developed during LZD administration than in those exhibiting hyponatremia before administration (34.0% vs. 18.8%) (Table 3).

Discussion

Vomiting is induced by multiple medical treatments and represents a significant reduction in a patient's quality of life. We reported that vomiting is associated with LZD administration in previous study [8]; therefore, we examined the risk factors for LZD-induced vomiting.

The overall incidence of vomiting was 18.1%, similar to that reported in a previous study (23.4%) [8]. The median time from the start of LZD administration to vomiting was consistent with previous reports [4–7]. Multiple logistic regression revealed that female sex, administration period (>10 days), and hyponatremia were independent risk factors for vomiting associated with LZD. In contrast, the concomitant use of serotonergic agents was an independent suppression factor for vomiting. Although renal impairment and being underweight are risk factors for thrombocytopenia [9–10], we found that LZD-induced vomiting was not associated with either of them.

The incidence of vomiting group was higher in women and was determined to be an independent risk factor. The mechanism of nausea and vomiting, especially CINV, is thought to involve multiple signalling pathways, including the D2, 5-HT3, and neurokinin 1 receptors [18]. D2 receptor sensitivity and expression were affected by oestradiol in female rats [23–24]. In addition, droperidol, a D2 receptor blocker, significantly prevented PONV in women in a randomised controlled trial (RCT) that included >5,000 patients [25]. These reports suggest a sex-associated difference in D2 receptor sensitivity. In contrast, the same RCT also reported that the menstrual cycle affects oestradiol concentration, but not the incidence of PONV [25]. Although the relationship between nausea and vomiting and sex is still controversial, female sex has been previously reported as a risk factor for PONV [17] and CINV [18].

The administration period (≥10 days) was significantly longer in the vomiting group. Lactic acidosis (LA) is an infrequent side effect of LZD; its primary symptoms include nausea and vomiting. A relationship between LA and LZD has been reported in several studies. The U.S. Food and Drug Administration (FDA) label information of Zyvox® states that LA is more likely when administered for more than 28 days [26]. In a recent study, LZD-induced LA occurred at 35 ± 29 days (mean ± standard deviation); its mechanism is hypothesises to include the inhibition of protein synthesis and aerobic respiration via mitochondrial ribosome malfunction [27]. Another study using the FDA Adverse Event Reporting System showed that numbers of reports regarding LA increased when LZD administration period exceeded 2 weeks [28]. These reports also support the hypothesis that LZD-induced vomiting is related to LA. However, the cut-off value for administration period in this study was defined as 10 days using the receiver operating characteristic (ROC) curve, which is shorter than the previous report [27–28], in which 20 patients received LZD for over 28 days. We were unable to assess the occurrence of LA in this study because very few patients underwent blood-gas analysis. Additional research is needed to determine the prevalence and mechanisms of LZD-induced LA.

Although there were no significant differences in the baseline incidence of hyponatremia between the two groups, the incidence increased in the vomiting group after LZD administration. Moreover, the severity of hyponatremia was higher in

the vomiting group (Table 1) and was more common in patients with hyponatremia after LZD administration (Table 3).

Hyponatremia has been identified as a risk factor for vomiting (Table 2). Its incidence was 18.1% in this study, which is similar to that in recent reports [20–21]. Considering the increased incidence and the high severity of hyponatremia in the vomiting group, it is possible that vomiting might be a symptom of hyponatremia that developed during LZD administration. However, vomiting is common even in patients without hyponatremia (Table 3); therefore, it cannot be explained by hyponatremia alone. It is also possible that hyponatremia developed as a consequence of vomiting rather than vomiting due to hyponatremia. However, we were unable to verify the temporal relationship between vomiting and hyponatremia because blood tests were not performed before the onset of vomiting in all cases; most patients underwent blood tests performed at least two days before or after the day they vomited. Therefore, we could only infer a relationship between vomiting and sodium levels by observing the lowest sodium levels. Thus, further studies are required to elucidate the association between vomiting and hyponatremia.

The concomitant use of serotonergic agents was negatively correlated vomiting; other medications did not affect vomiting (Table 2). First, we hypothesised that concomitant use of serotonergic agents, such as SSRIs, with LZD could induce vomiting via an augmented release of 5-HT and stimulation of 5-HT receptors, but the opposite effect was observed. In this study, trazodone and SSRIs were the most commonly used serotonergic agents in 21 and 20 cases, respectively (duplicated cases existed). Trazodone usage also includes single-dose administration, as for hypnotics; however, it was unclear whether trazodone was regularly administered. In addition to its SSRI-like effect, trazodone also inhibits 5-HT2A, 5-HT2B, and 5-HT2C receptors [29]. In particular, inhibition of 5-HT2C receptors contributes to a CINV prophylactic effect, similar to that of olanzapine [30]. Considering these effects, it is possible that trazodone has an antiemetic effect similar to that of olanzapine. SSRIs have been reported to desensitise 5-HT receptors such as 5-HT2C and 5-HT3 [31]. This may contribute to a reduction in the incidence of vomiting associated with LZD. In this study, drugs that increase 5-HT secretion were defined as serotonergic agents, but several of these have multiple 5-HT receptor antagonistic mechanisms, such as mirtazapine [32]. Considering these mechanisms, it is possible that serotonergic agents may have an antiemetic effect via desensitisation or blocking of various 5-HT receptors.

We observed no difference in the proportions of patients who concomitantly used D2 receptor blockers at baseline between the two groups; so it is possible that LZD-induced vomiting was not suppressed by D2 receptor blockers. RFP was not detected as a risk or suppression factor. Since RFP decreases the LZD blood concentration, LZD concentration may not be related to the occurrence of LZD-induced vomiting [16]. This hypothesis is also supported by our finding that “renal impairment (Ccr <60 mL/min) and low body weight (<40 kg)”, which are factors that generally increase the blood LZD concentration, were not associated with LZD-induced vomiting [9–10].

This study has several limitations. First, it was a single-centre retrospective observational study. Second, the patients were not followed up after discontinuation of LZD. It is necessary to determine if the patients experienced nausea or any improvement in vomiting. However, as nausea is a subjective symptom it is difficult to evaluate its presence, absence, and severity from electronic medical records. Third, our study did not reach EPV ≥10, that is, the number of cases enrolled was 496 and the number of factors applied in multivariate analysis was 11. Thus, the accuracy and precision of logistic regression may decrease [13]. It is necessary to perform an additional study by increasing the number of subjects. Fourth, other causes of vomiting, such as comorbidities and concomitant medications, could not be completely excluded. Drugs administered as a single dose, such as anti-emetics, are also defined as concomitant medications; however, it was not clear whether a single dose was regularly administered. Therefore, to exclude confounding effects, our evaluations excluded the concomitant use of 5-HT agonists, opioids, tramadol, and RFP. The incidence of vomiting was 17.0% (56 of 328 cases), which was almost the same as the overall incidence of vomiting. This result supports the hypothesis that LZD administration induces vomiting.

We succeeded in identifying risk factors for LZD-induced vomiting for the first time, including female sex, long-term administration, and the development of hyponatremia. Among them, long-term administration may be associated with LA and may be life-threatening. However, the causes of vomiting often cannot be identified because multiple factors coexist, and it must be considered that there are many cases in which LZD administration was discontinued due to lack of tolerance. Recently,

some studies have reported that the incidence of hyponatremia in patients receiving LZD is approximately 20% [20–21]. This is consistent with the results of the present study. Since hyponatremia is known to cause vomiting, it may exist as a background factor during LZD administration. Because vomiting occurs as a result of complex biological reactions, causes related to LZD are not limited to the risk factors identified in this study. Improved management of these side effects is expected to support safer and more sustainable LZD treatment.

Declarations

Authors' Contribution

Study concept and design: Takezo Tsutsumi, Shungo Imai, and Yoh Takekuma; acquisition of data: Takezo Tsutsumi; analysis and interpretation of data: all authors; drafting the manuscript: Takezo Tsutsumi; revising the manuscript critically for important intellectual content: All authors. All the authors approved the version of the manuscript.

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Conflicts of interest/Competing interests

The authors declare no conflicts of interest.

Availability of data and material

The datasets generated during and analysed during the current study are available from the corresponding author upon reasonable request.

Code availability

Not applicable.

Ethics approval

This study was approved by the Institutional Review Board of the Hokkaido University Hospital for Clinical Research (study protocol NO. 019-0213).

Consent to participate

Not applicable.

Consent for publication

Not applicable

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TABLES

Table 1 Comparison of the characteristics between patients with vomiting and without vomiting

	Vomit (n = 90)	Non-Vomit (n = 406)	*P* value
Age (year), median (range)	61.5 (20–89)	62 (20–89)	0.98
Age (year), ≥65, n (%)	37 (41.1)	175 (43.1)	0.73
Sex (female), n (%)	50 (44.4)	135 (33.5)	<0.01*
Body weight (kg), median (range)	55.4 (35.9–110.0)	60.0 (32.4–118.1)	0.02*
Body weight (kg) <40, n (%)	6 (6.67)	19 (4.68)	0.43
Administration period of LZD (days), median (range)	14 (4–64)	10 (4–41)	<0.01*
Intravenous infusion of LZD, n (%)	56 (62.2)	238 (58.6)	0.53
Baseline S-Na (mEq/L), median (range)	138 (128–151)	139 (116–182)	0.03*
Minimum S-Na (mEq/L), median (range)	133.5 (116–146)	136 (116–172)	<0.01*
Baseline S-Na ≤134 mEq/L, n (%)	18 (20.0)	78 (19.2)	0.88
With hyponatremia (S-Na ≤134 mEq/L), n (%) [a]	36 (40.0)	70 (17.2)	<0.01*
Grade1 (134≥ S-Na ≥130 mEq/L), n (%)	21 (23.3)	56 (13.8)	0.02*
Grade2 (130> S-Na ≥125 mEq/L), n (%)	8 (8.9)	12 (3.0)	0.02*
Grade3 (125> S-Na ≥120 mEq/L), n (%)	4 (4.4)	2 (0.5)	0.01*
Grade4 (S-Na <120 mEq/L), n (%)	3 (3.3)	0 (0)	<0.01*
Serum creatinine (mg/dL), median (range)	0.89 (0.19–9.5)	0.82 (0.2–12.5)	0.90
Creatinine clearance (mL/min), median (range)	62.3 (5.6–369.8)	69.1 (4.0–438.3)	0.19
With renal impairment (Ccr <60 mL/min), n (%)	44 (48.9)	167 (41.1)	0.18
Concomitant baseline use of dopamine D2 blockers, n (%)	11 (12.2)	75 (18.5)	0.17
Concomitant use of serotonergic agents, n (%)	3 (3.3)	38 (9.4)	0.09
Concomitant use of opioids, n (%)	21 (23.3)	78 (19.2)	0.38
Concomitant use of tramadol, n (%)	11 (12.2)	49 (12.1)	1.00
Concomitant use of RFP, n (%)	13 (14.4)	26 (6.4)	0.02*
With operations, n (%)	21 (23.3)	64 (15.8)	0.08
With chemotherapy, n (%)	5 (5.6)	23 (5.7)	1.00

LZD, linezolid; S-Na, serum sodium level; Ccr, creatinine clearance; RFP, rifampicin

*Statistical significance was set at $p < 0.05$.

[a] Hyponatremia was defined as baseline S-Na >134 mEq/L and reduced to ≤134 mEq/L after LZD administration.

342 **Table 2** Univariate and multivariate analysis for risk factors of LZD-induced vomiting

	Univariate			Multivariate		
	OR	95% CI	*P* value	aOR	95% CI	*P* value
Age (year) ≥65, n (%)	0.92	0.58–1.46	0.73			
Sex (female), n (%)	2.51	1.58–4.01	<0.01†	2.69	1.62–4.47	<0.01*
Body weight (kg) <40, n (%)	1.45	0.56–3.75	0.44			
Intravenous infusion of LZD, n (%)	1.16	0.73–1.86	0.53			
Administration period of LZD (days) ≥10, n (%)	2.89	1.71–4.89	<0.01†	2.57	1.46–4.50	<0.01*
With hyponatremia (S-Na ≤134 mEq/L), n (%) [a]	3.20	1.95–5.24	<0.01†	2.96	1.72–5.10	<0.01*
With renal impairment (Ccr <60 mL/min), n (%)	1.37	0.87–2.16	0.18†	1.25	0.75–2.06	0.39
Renal replacement therapy, n (%)	1.284	0.61–2.70	0.507			
Concomitant baseline use of dopamine D2 blockers, n (%)	0.61	0.31–1.21	0.16†	0.71	0.34–1.47	0.36
Concomitant use of serotonergic agents, n (%)	0.33	0.10–1.11	0.07†	0.23	0.07–0.82	0.02*
Concomitant use of opioids, n (%)	1.28	0.74–2.21	0.38	1.27	0.70–2.30	0.44
Concomitant use of tramadol, n (%)	1.01	0.50–2.04	0.97	0.86	0.39–1.86	0.69
Concomitant use of RFP, n (%)	2.47	1.21–5.02	0.01†	2.02	0.88–4.63	0.11
With operations, n (%)	1.63	0.93–2.84	0.09†	1.25	0.65–2.39	0.50
With chemotherapy, n (%)	0.98	0.36–2.65	0.97	1.16	0.40–3.40	0.79

343 LZD, linezolid; S-Na, serum sodium level; Ccr, creatinine clearance; RFP, rifampicin; OR, odds ratio; aOR, adjusted odds
344 ratio; CI, confidence interval.

345 † These variables were incorporated into the multivariate analysis.

346 * Statistical significance was set at $P < 0.05$.

347 [a] Hyponatremia was defined as baseline S-Na >134 mEq/L and reduced to ≤134 mEq/L after LZD administration.

348

Table 3 Incidence of vomiting in patients with hyponatremia

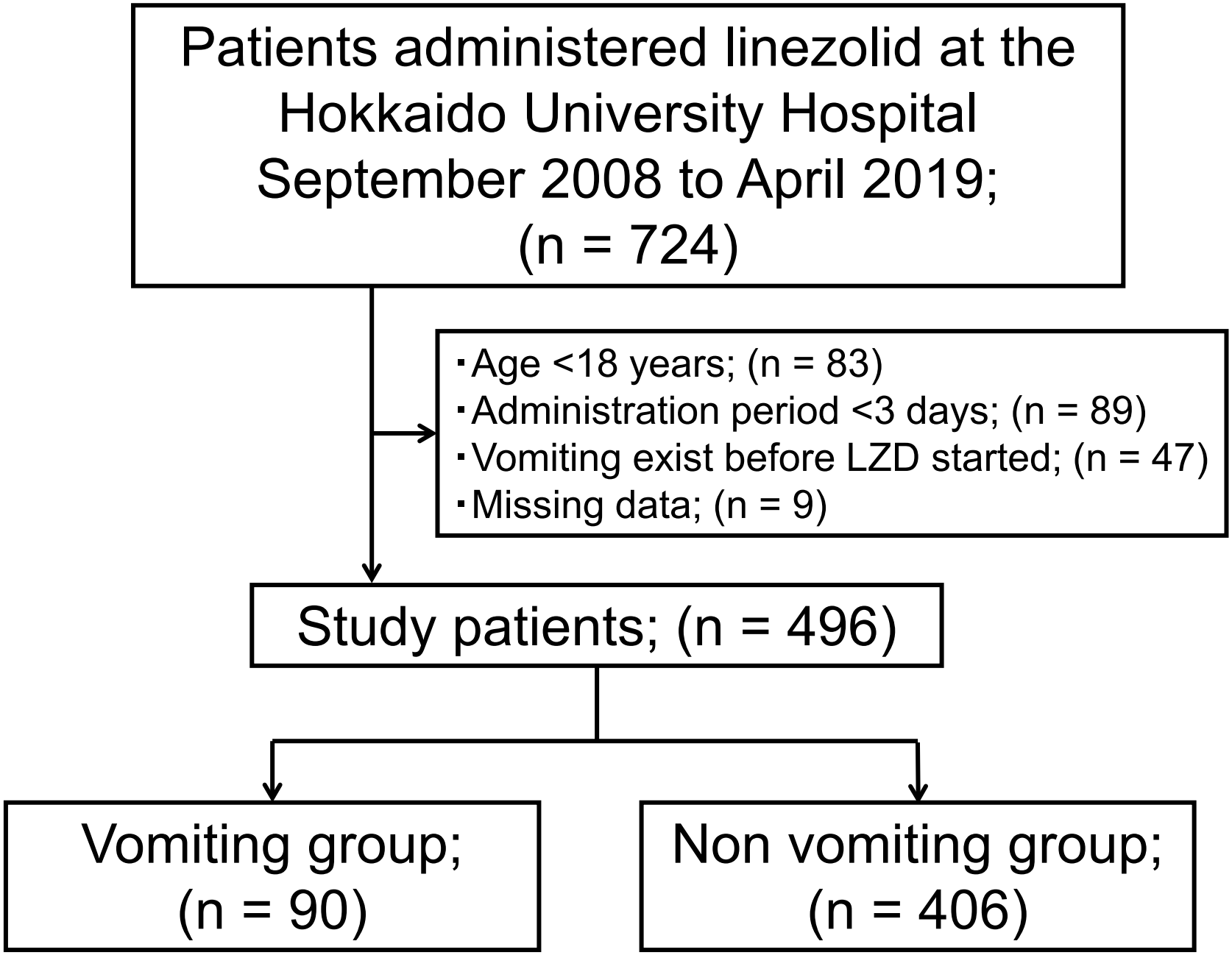
	Incidence of vomiting, n (%)
All hyponatremia patients in this study (n = 202)	54 (26.7)
With hyponatremia before LZD administration (n = 96)	18 (18.8)
With hyponatremia during LZD administration (n = 106)	36 (34.0)
No hyponatremia episode (n = 294)	36 (12.2)

LZD, linezolid

353 **FIGURE LEGENDS**

354

355 **Fig. 1** Flowchart of patients included in this study


Patients administered linezolid at the Hokkaido University Hospital September 2008 to April 2019; (n = 724)
・Age <18 years; (n = 83)
・Administration period <3 days; (n = 89)
・Vomiting exist before LZD started; (n = 47)
・Missing data; (n = 9)
Study patients; (n = 496)
Vomiting group; (n = 90)
Non vomiting group; (n = 406)