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CASE REPORT

Therapeutic Dose Monitoring for Linezolid in a Patient with MRSA Pneumonia with Bacteremia in Diabetes Insipidus

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ABSTRACT

Introduction: Few studies have investigated the effect of increased creatinine clearance (CrCl) on linezolid (LZD) concentration. Herein, we report the pharmacokinetic/pharmacodynamic (PK/PD) profile of LZD used in the management of methicillin-resistant *Staphylococcus aureus*

(MRSA) pneumonia with concomitant bacteremia in a patient with high CrCl caused by diabetes insipidus (DI).

Case Report: A 19-year-old man was admitted to the intensive care unit following a traumatic brain injury. After admission, he underwent a craniotomy for the severe brain injury. However, he developed DI after the operation. Despite treatment with vasopressin, his urine output reached 5–6 L/day as a result of the DI, and his CrCl increased to 180–278 mL/min. We were required to administer 6–7 L of fluid a day to compensate for the high urinary fluid output. On day 55, MRSA pneumonia with sepsis was suspected and, consequently, LZD was administrated intravenously (600 mg every 12 h). He was treated with LZD for 14 days. The patient has since successfully recovered from MRSA pneumonia with concomitant bacteremia, and was transferred to the general ward on day 82. Blood LZD levels from days 60–68, which were measured after the patient's transfer to the general ward, showed that the trough levels were lower than the threshold level of detection. The blood 24-h area under the plasma LZD concentration–time curve $(AUC)_{24}$/minimum inhibitory concentration (MIC) was 69.3.

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Conclusion: In spite of the low level of LZD AUC$_{24}$/MIC caused by the high CrCl with DI, MRSA pneumonia with concomitant bacteremia was successfully treated with LZD.

Keywords: Area under the plasma drug concentration–time curve/minimum inhibitory concentration; Bacteremia; Blood concentration; Diabetes insipidus; Linezolid; Methicillin-resistant *Staphylococcus aureus*; Pneumonia

INTRODUCTION

Linezolid (LZD) is an oxazolidinone antibiotic characterized by a wide spectrum of activity against Gram-positive pathogens resistant to β-lactams and glycopeptides, and its use has progressively increased in recent years [1, 2]. LZD clearance is mainly non-renal (approximately 65%) through the formation of two major inactive metabolites, the hydroxyethyl glycine metabolite (PNU-142586) and the aminoethoxyacetic acid metabolite (PNU-142300), which account for 40–50% and 9–10% of the total dose, respectively. Renal clearance of the unchanged parent drug accounts for the remaining 30–40% [3]. More recent reports have suggested that the influence of renal dysfunction on high LZD blood concentration may lead to hematological side effects such as thrombocytopenia [8, 9].

However, the influence of low LZD blood concentration in conjunction with high creatinine clearance (CrCl) still remains unknown. Additionally, the pharmacokinetic/pharmacodynamic (PK/PD) index for the efficacy of LZD was previously shown to be a 24-h area under the plasma LZD concentration–time curve/minimum inhibitory concentration (AUC$_{24}$/MIC) ratio of ≥100 [4–6]. Herein, we report the PK/PD profile of a patient with methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia and bacteremia who developed diabetes insipidus (DI) with a high level of CrCl. Despite the low AUC$_{24}$/MIC of LZD in comparison with the efficacy level of AUC$_{24}$/MIC (≥100) [4–6], the patient was successfully treated for the MRSA infection.

CASE REPORT

Sampling and Drug Administration

Blood samples for the quantification of LZD in plasma were collected through an indwelling arterial catheter both before and after the morning dosing, which was administered through an intermittent intravenous infusion of 600 mg over the course of 1 h. LZD was administered twice a day (morning and night). Blood samples were taken in the morning before dosing (trough) and after the morning's 1-h-long LZD administration. After centrifugation, plasma samples were separated and stored at −80 °C until assayed. Blood LZD concentration was measured after the patient's transfer to the general ward.

Creatinine Clearance

To assess renal function, creatinine concentrations in both the serum and 24-h urine samples were determined. CrCl (mL/min) was calculated using the formula:

$$\text{CrCl} = (C_{\text{urine}} \times V_{\text{urine}})/(C_{\text{serum}}) \times (1.73/\text{BSA})$$

where C_{urine} (mg/dL) is the creatinine concentration in urine, V_{urine} (mL/min) is the urine volume, C_{serum} (mg/dL) is the serum creatinine concentration, and BSA (m^2) is the body surface area.

LZD Assay

LZD blood concentration was measured through high-performance liquid chromatography [7]. The lower limit of the quantification was 0.5 mg/L.

Pharmacokinetic Assessment

A PK analysis of LZD was performed using the nonlinear least squares program MULTI [8]. The drug concentration data were fit to a standard one-compartment model with zero-order input (1-h-long drug infusion) and first-order elimination. The PK parameters used were total clearance (L/h) and volume of distribution (L). The LZD AUC_{24} was estimated using PK parameters for daily dose/total clearance.

Case

A 19-year-old male was admitted to Fukuoka University Hospital after being involved in a traffic accident. A neurological assessment revealed a Glasgow Coma Scale (GCS) score of 3/15. Computed tomography (CT) of the head showed a subcutaneous and extradural hematoma. A craniotomy was immediately performed to remove the hematoma and to attain cerebral decompression and, as a result, the GCS score recovered to 10/15. On day 13, he developed polyuria. His 24-h urine volume reached 5–6 L/day with a urine osmolality of 159 mOsm/L and a plasma osmolality of 340 mOsm/L. Thus, he was diagnosed with cerebral DI. As a basal skull fracture was present, an intravenous vasopressin infusion was administered to treat the DI. However, it showed a poor therapeutic effect, polyuria continued, and CrCl was revealed to be 180–278 mL/min as a result of the DI. We were required to administer approximately 6–7 L/day of fluid to compensate for the high urinary fluid output. On day 50, MRSA was detected in surveillance cultures of sputum and urine samples (MIC for LZD was 1 mg/L).

On day 55, he developed systemic inflammatory response syndrome (SIRS) [9], and pneumonia and/or a urinary tract infection was suspected based upon the results of preceding surveillance cultures. Consequently, LZD was administrated intravenously (600 mg every 12 h) for 14 days. On day 57, a chest X-ray and CT scan showed a consolidation in the right lung (Fig. 1a, b). It was found that blood cultures that had been drawn before the administration of LZD developed MRSA (MIC for LZD was 1 mg/L) while the cerebrospinal fluid culture was negative. In transthoracic echocardiography, there was no evidence of infectious endocarditis at day 56. Based upon these findings, we diagnosed MRSA pneumonia with secondary bacteremia due to pneumonia or a urinary tract infection. Blood, urine, and sputum cultures were negative on days 61, 64, and 68, respectively. A chest X-ray on day 68 and CT scan on day 70 showed improvement in the consolidation (Fig. 1c, d). The patient was successfully transferred to the general ward on day 82. Concomitant antibiotics were not administered because the results of the cultures showed the development of MRSA only (Fig. 2).

Blood concentrations of LZD from days 60–68 were measured after the patient's transfer to the general ward. The AUC_{24}/MIC values over the observation period were found to be 69.3 2 days after LZD administration, and the trough levels were too low to be detected (Fig. 2).
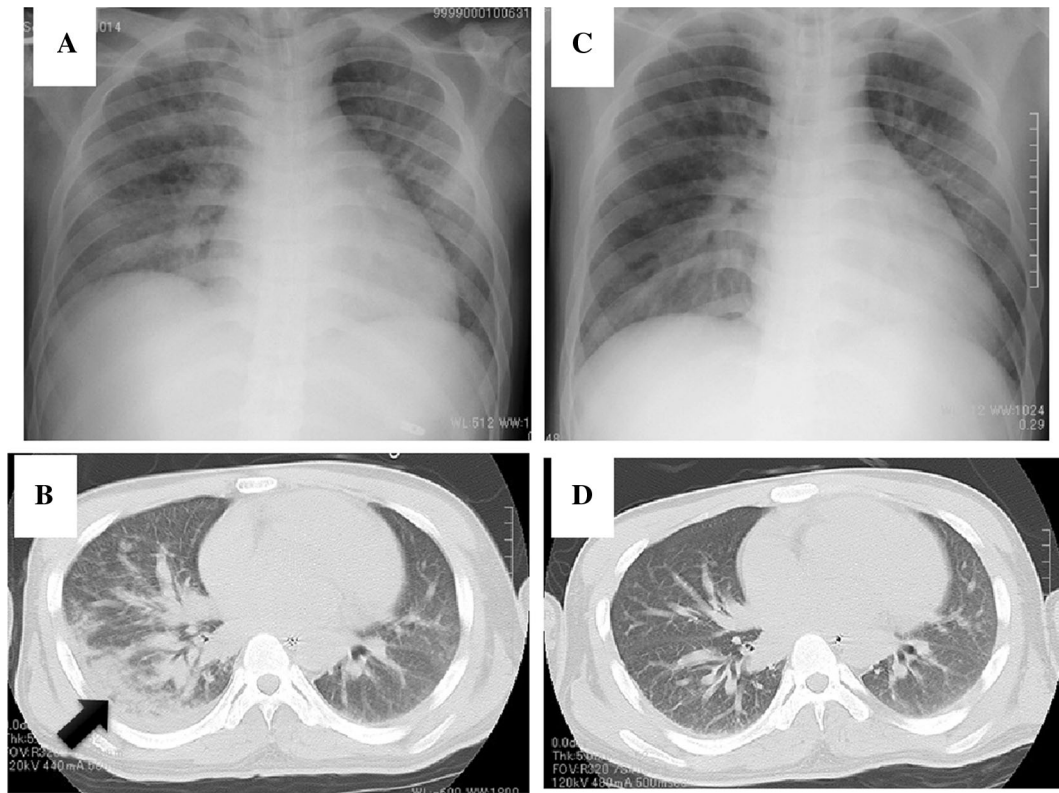
Fig. 1 Chest imaging before and after treatment with LZD. a (Chest X-ray) and b (chest CT scan; day 57) show consolidation in right lower lung before treatment (b, arrow). c The chest X-ray (day 68) and d shows the chest CT scan (day 70) images after treatment, and show the improvement in the consolidation

Informed consent was obtained from the patient's family in relation to his being included in the study.

DISCUSSION

To the best of our knowledge, this is the first case to report a PK profile of LZD in a patient with DI with high CrCl. In this case, CrCl was 180–278 mL/min as a result of DI. In regard to patients with a high level of CrCl in the intensive care unit, it was reported that blood LZD concentrations were variable, showing trough concentrations from 0.13 to 14.49 mg/ L (median 2.06 mg/L) [10]. In the current case, blood LZD trough levels were lower than the detection limit (<0.5 mg/L) and the AUC_{24}/MIC

(69.3) was also remarkably low compared with those provided in previous reports concerning 20 critically ill patients (median 248 mg/L, interquartile range 144–347 mg/L) [11]. Since the LZD trough levels were lower than the detection limit (0.5 mg/L), the actual AUC_{24}/ MIC may have been lower than that in our calculated AUC_{24}/MIC levels. The precise mechanism of the decreased LZD AUC_{24}/MIC and blood trough levels in this case is unknown; however, LZD PK might be altered by high CrCl and a large volume of fluid administration.

In the current case, we diagnosed MRSA pneumonia for the following reasons. First, the precedent surveillance culture of sputum only developed MRSA and no other significant microorganisms; second, the chest CT scan
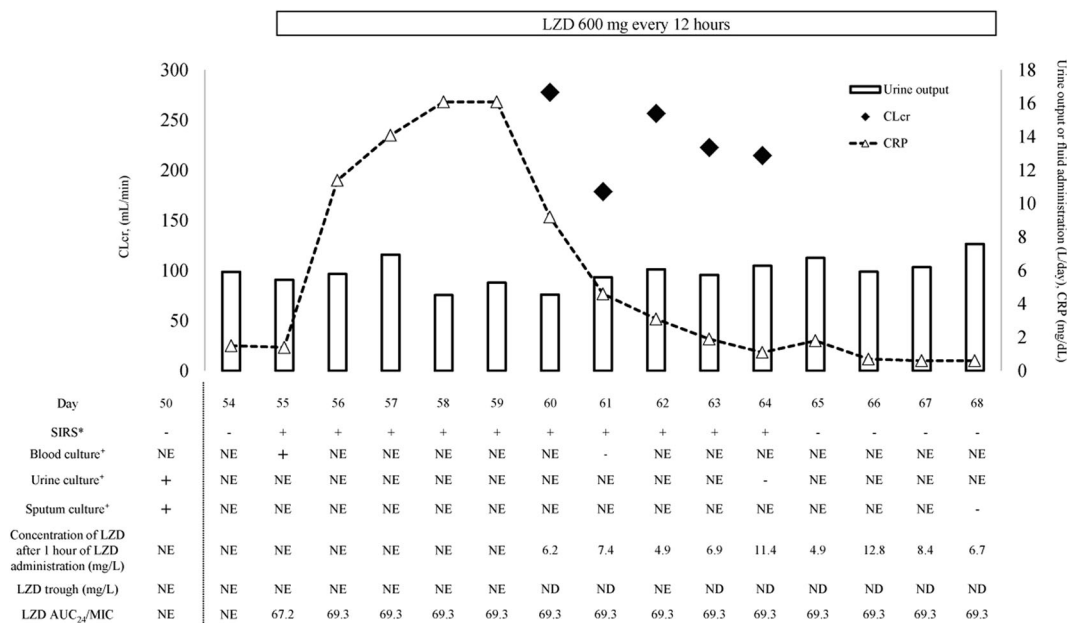
LZD 600 mg every 12 hours

Day	50	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68
SIRS*	-	-	+	+	+	+	+	+	+	+	+	+	-	-	-	-
Blood culture+	NE	+	NE	NE	NE	NE	NE	NE	-	NE	NE	NE	NE	NE	NE	NE
Urine culture+	+	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-	NE	NE	NE	NE
Sputum culture+	+	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	-
Concentration of LZD after 1 hour of LZD administration (mg/L)	NE	NE	NE	NE	NE	NE	NE	6.2	7.4	4.9	6.9	11.4	4.9	12.8	8.4	6.7
LZD trough (mg/L)	NE	NE	NE	NE	NE	NE	NE	ND	ND	NE	ND	ND	ND	ND	ND	ND
LZD AUC_{24}/MIC	NE	NE	67.2	69.3	69.3	69.3	69.3	69.3	69.3	69.3	69.3	69.3	69.3	69.3	69.3	69.3

Fig. 2 Clinical course and LZD blood concentration. *Asterisk* A '+' indicates at least two SIRS criteria [9]. *Plus* A '+' indicates that MRSA developed in the culture; a '−' shows that nothing grew in the culture. LZD (600 mg) was administered twice a day for 1 h. The concentration of LZD was shown before the day's first administration (trough) and after the first 1-h LZD administration for the day. CrCL (mL/min) was calculated using the formula: $CrCl = (C_{urine} \times V_{urine})/(C_{serum}) \times (1.73/BSA)$; where C_{urine} (mg/dL) is the creatinine concentration in urine, V_{urine} (mL/min) is the urine volume, C_{serum} (mg/dL) is the serum creatinine concentration, and BSA (m^2) is the body surface area. AUC_{24}/MIC 24-h area under the plasma linezolid concentration–time curve/minimum inhibitory concentration, *CrCl* creatinine clearance, *CRP* C-reactive protein, *LZD* linezolid, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ND* not detected, *NE* not examined, *SIRS* systemic inflammatory syndrome

showed a consolidation in the right lower lung, which suggested a transbronchial route of infection; and third, the pneumonia was successfully treated with LZD only, not with any other antimicrobials. An American consensus review [12] recommended vancomycin for the treatment of MRSA infections; however, in a randomized-controlled study for MRSA nosocomial pneumonia, LZD showed better clinical efficacy and microbiological responses than vancomycin [13]. Rayner et al. [5] reported that higher success rates for LZD may occur at AUC_{24}/MIC values of 80–120 for bacteremia, skin and skin structure infections, and lower respiratory tract infections. In this case, on day 50, the urine culture developed MRSA ≥10^6/colony-forming units/mL. It is unclear whether the patient had a urinary tract infection or if the observed MRSA in the urine had simply passed into the urine from the blood. Additionally, on day 64, MRSA was not detected in the urine culture. To the best of our knowledge, little investigation has been conducted into the usefulness of LZD for the treatment of urinary tract infections [14]. Approximately 35% of LZD is excreted in urine [14]. In this case, a high level of urine output was observed because of DI and, consequently, the high doses of LZD may be passed though the urinary tract. Therefore, despite low plasma LZD AUC, the urine culture may become negative. Interestingly, in spite of the remarkably low level of the AUC_{24}/

MIC in this case, MRSA pneumonia bacteremia was treated successfully after LZD administration. In LZD, the level of plasma protein binding is 31% and the volume of distribution approximates the total water content of the body (40–50 L) [15, 16]. In lung tissues, it was reported that LZD concentrations in the epithelial lining fluid (64.3 ± 33.1 μg/mL) were much higher than those in the blood (7.3 ± 4.9 μg/mL) and alveolar cells (2.2 ± 0.6 μg/mL) [17]. These findings suggest that LZD is excluded or rapidly removed from the blood to the lung compartment. As this was a retrospective study, we could not examine the concentration of LZD in the epithelial lining fluid. For this reason we could not take cultures and blood samples every day.

To our knowledge, this is the first report showing the successful treatment of MRSA pneumonia with bacteremia despite very low LZD AUC_{24}/MIC. Localized higher concentrations of LZD in the lung might have been sufficiently effective in treating the pneumonia and the secondary bacteremia as a result of the sites of these infections; however, the precise mechanism of low LZD AUC_{24}/MIC and successful treatment of MRSA infection in these cases remains generally unknown.

CONCLUSIONS

In conclusion, sub-therapeutic levels of LZD blood concentrations may be caused by uncontrolled DI with high CrCl and a high level of fluid administration. In spite of the low level of AUC_{24}/MIC, MRSA pneumonia and bacteremia were successfully treated with LZD. As this was a retrospective study, we were unable to evaluate the concentration of LZD

on days 60–68 after the 1-h LZD administration for the PK assessment. We must further study the actual PK assessment of LZD in patients with high CrCl caused by DI. Further investigation is required into the mechanisms of low LZD AUC_{24}/MIC and the successful treatment of these MRSA infections.

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Compliance with ethics guidelines. Informed consent was obtained from the patient's family in relation to his being included in the study.

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