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Case Report

Pharmacokinetics of linezolid during continuous hemodiafiltration: A case report

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ABSTRACT

The pharmacokinetics of linezolid clearance (CL_{LZD}) during continuous hemodiafiltration (CHDF) has not been comprehensively analyzed. Here, we examined CL_{LZD} by CHDF in a patient with septic shock and disseminated intravascular coagulation due to methicillin-resistant *Staphylococcus aureus*. The extraction ratio of LZD by CHDF was 22.6%, and the protein-binding rate was 17.9% ± 7.7%. In addition, it was determined that the calculated total body clearance of LZD was 30.2 mL/min, plasma elimination half-life was 8.66 h, and the CL_{LZD} by the dialyzer used for CHDF was 23.0 mL/min. From the obtained pharmacokinetics, the CL_{LZD} of patients continuing CHDF was estimated to be approximately half of the reported CL_{LZD} for healthy subjects. In addition, the LZD concentration of the sepsis patient who underwent CHDF remained higher than the minimum inhibitory concentration and was similar to the LZD concentrations reported in normal renal function patients. Although further studies are warranted, when LZD is administered to patients treated with CHDF, the present findings suggest that dose regulation is not required.

1. Introduction

Continuous renal replacement therapy (CRRT) is frequently used to treat critically ill patients with acute renal failure due to severe infections [1–3], which typically require treatment with antimicrobial agents [4]. For this reason, solute removal dialysis is essential in such patients. However, in patients receiving hemodialysis, such as intermittent hemodialysis or CRRT, the optimal dosage and administration of recommended antibiotics remains unclear based on clinically available data.

Linezolid (LZD) is a novel synthetic antimicrobial agent consisting of an oxazolidinone backbone and has an action site distinct from existing agents [5]. LZD is used for the treatment of potentially fatal infectious diseases caused by drug-resistant Gram-positive cocci [6]. In healthy subjects, 50%–70% of LZD is metabolized by the liver into two major metabolites, which are then excreted by the kidney [7]. Based on the pharmacokinetic profiles of LZD, dose adjustment is not considered to be necessary for patients with moderate liver or renal dysfunction, as LZD is predominantly metabolized into an active form through oxidation of its morpholine ring in non-enzymatic reactions [8]. Because LZD has a low molecular weight (337 Da), the serum levels of LZD may be markedly reduced in patients receiving continuous (24 h/day) renal replacement therapy, resulting in subtherapeutic serum concentrations and treatment failure. To date, however, few reports have examined LZD clearance (CL_{LZD}) and other pharmacokinetic parameters during CRRT [4,9], particularly continuous hemodiafiltration (CHDF), which is used frequently in Japan [10].

In the present case report, we examined the pharmacokinetics of LZD during CHDF in a patient who received LZD for septic shock with disseminated intravascular coagulation (DIC) due to methicillin-resistant *Staphylococcus aureus* (MRSA). In addition, the CL_{LZD} during CHDF was measured to determine whether the effective treatment concentration of LZD was maintained during CHDF.

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2. Case report

A 64-year-old Japanese male (height, 172.0 cm; weight: 61.1 kg) was diagnosed with septic shock due to purulent spondylitis and DIC and was admitted to our hospital. Meropenem hydrate (MEPM), clindamycin, minocycline and vancomycin (VCM) were immediately administered after hospitalization, and CHDF using a direct hemo-perfusion membrane hemofilter was started. The patient's background and laboratory values on admission are presented in Table 1. Each measured parameter was outside of the normal range. The diagnosis of sepsis was confirmed by the positive detection of MRSA in cultures of venous blood. During the patient's hospital stay, continuous renal replacement therapy (24 h/day) was tolerated without complications. However, because the urinary volume during CHDF period was ≤19 mL, the patient was considered to have low residual renal function. On the tenth day of hospitalization, the continuously administered antibiotics were discontinued, and MEPM and LZD combination therapy was started. The patient received 3000 mg MEPM by intravenous (IV) infusion over 60 min every 8 h, and 600 mg LZD by IV infusion over 60 min every 12 h for 4 days. Blood was collected immediately before administration starting on day 2 and was then collected every day during the LZD administration period. After 4 days of LZD therapy, MRSA was no longer detectable from blood cultures and the CRP blood test used to detect inflammation or infection was stable; therefore, LZD administration was discontinued.

2.1. CHDF procedure

A CHDF circuit (TR-525, Jun-Ken Medical Co., Tokyo, Japan) using a 1.0-m^2 surface-treated acrylonitrile and sodium methallyl sulfonate copolymer filter (sepXiris, Baxter, Inc., Tokyo, Japan). The blood flow rate was maintained at 80 mL/min throughout the treatment period. Dialysate/replacement fluid (Sublood-BSG, Fuso Pharmaceutical Industries, Ltd., Tokyo, Japan) was infused in the arterial line and replacement was done by infusion into the dialysis catheter at initial flow rates of 500 and 300 mL/h, respectively. The flow rate was not changed during LZD treatment, and the effluent rate was held at 1000 mL/h.

2.2. Blood sampling

A blood sample was collected 30 min after the first dose of LZD was administered on day 2 (C1). Blood samples were then collected every 12 h just prior to LZD administration (C2–C4). To examine the CL_{LZD} by the CHDF (CL_{CHDF}), samples of filter inlet ($C2_{inlet}$) and outlet blood ($C2_{outlet}$) were also collected immediately before the second administration of LZD on day 2, and samples C3 and C4 in the following 12 and 24 h. All samples were immediately transported on ice to the laboratory, where they were centrifuged at 1700 × *g* for 10 min, frozen and stored at −80 °C until needed for analysis.

Table 1
Patient background and laboratory values on admission.

Underlying disorder		
Type II diabetes mellitus Purulent spondylitis		
Parameter	Measured value	Standard value
ALB (g/dL)	2.3	4.1–5.1
CRP (mg/dL)	23.39	≤0.14
WBC (× 10^9/L)	6.10	3.3–8.6
BUN (mg/dL)	60.9	8.0–20
SCr (mg/dL)	3.47	0.65–1.07
AST (IU/L)	195	13–30
ALT (IU/L)	95	10–42
PCT (ng/mL)	85.6	≤0.3

ALB, albumin; CRP, C-reactive protein; WBC, white blood cell count; BUN, blood urea nitrogen; SCr, serum creatinine, AST, aspartate aminotransferase; ALT, alanine aminotransferase; PCT, procalcitonin.

2.3. Determination of LZD concentrations

Bulk LZD powder for high-performance liquid chromatography (HPLC) was purchased from Pfizer Inc. All other reagents were analytical grade and were commercially available. The samples of serum and plasma for pharmacokinetic analysis were stored at −80 °C until needed for analysis. Serum and plasma were deproteinized with an equivalent volume of acetonitrile and then separated by centrifugation for 15 min at 14,000 × *g*. The obtained supernatant was measured by HPLC using the absolute calibration method. Unbound LZD in the collected serum and plasma specimens was obtained by centrifugation of 250 μL of the serum or plasma specimens with a Centrifree Ultrafiltration device (Merck Millipore Ltd., Cork, Ireland) for 30 min at 2000 × *g*. Each sample was injected into the HPLC system. Total and unbound LZD concentrations in serum and plasma were determined by an HPLC method with ultraviolet (UV) detection. The HPLC system (LC-2010; Shimadzu Corp., Kyoto, Japan) consisted of a pump, autosampler, UV detector and column oven. Data were collected and analysed using LC solution. Separation was performed on an octadecyl silane (ODS) hypersil column (Cadenza 5CD-C18, 150 mm × 4.6 mm, 5 μm; Imtakt Co., Kyoto, Japan). A solution of 1% orthophosphoric acid, 30% methanol, and 2 g/L heptane sulfonic acid (1:30:69) was used as the mobile phase, and the pH was adjusted to 5 by the addition of 10 M sodium hydroxide. The pump flow rate was 1.0 mL/min and the column temperature was maintained at 40 °C. The UV detection wavelength was set at 254 nm. Calibration curves were linear over a concentration range of 0.1–50 μg/mL for total and unbound LZD. The intra/inter-day coefficient of variation (CV) was below 5.0%, and the lower limit of quantification (LLOQ) was 0.1 μg/mL for both total and unbound LZD.

2.4. Calculations

Standard equations were used to calculate the pharmacokinetic (PK) parameters of half-life ($T_{1/2}$), elimination rate, and volume of distribution (Vd). Total clearance (CL_{tot}) was calculated by dividing the dose by the area under the concentration curve ($AUC_{0-\infty}$), which represents the AUC versus the time curve. $AUC_{0-\infty}$ was calculated by the total (free and protein bound) LZD concentration. The CL_{CHDF} was calculated using the following equation:

$$CL_{CHDF} = \frac{(QBin \times CBin) - (QBout \times CBout)}{CBin}$$

CBin: LZD concentration on the blood inlet side of the dialysis membrane (mg/L); *CBout*: LZD concentration of the blood outlet side of the dialysis membrane (mg/L); *QBin*: Blood side inlet flow rate (mL/min); *QBout*: Blood side outlet flow rate (mL/min).

The calculated PK parameters are shown in Table 2. The Vd and $T_{1/2}$ of LZD were 19.35 L and 8.66 h, respectively. Based on these values, the estimated Ke and $AUC_{0-\infty}$ were 0.09 h and 332.3 mg h/L, respectively, and CL_{tot} and CL_{CHDF} were 30.2 mL/min and 23.0 mL/min, respectively. The average serum trough blood concentration, free LZD concentration, and protein binding rate of LZD during CHDF enforcement (C3–C4) were 16.1 ± 2.0 μg/mL, 13.1 ± 1.4 μg/mL, and 17.9 ± 7.7 (%), respectively (Table 3).

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