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Single-dose linezolid pharmacokinetics in critically ill patients with impaired renal function especially chronic hemodialysis patients†

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ABSTRACT: *Background and Objective:* Renal failure patients were treated with linezolid (LZD) for proven or suspected infections by multi-resistant Gram-positive cocci. The aim of this study was to determine if dose adjustment of LZD is needed as a function of renal impairment or not, especially that a significant component of LZD is eliminated unchanged in urine. *Methods:* The single dose pharmacokinetics of LZD was investigated. Eighteen non-infected male subjects with various degrees of renal impairment ranged from normal to severe chronic impairment were enrolled, including end-stage renal disease (ESRD) patients maintained on hemodialysis (HD). LZD was administered as a single oral 600 mg dose, and blood samples were drawn at different times and analysed by a validated HPLC assay method. Plasma profiles were evaluated by non-compartmental and compartmental approaches. *Results and Discussion:* A similar rate and extent of LZD absorption and elimination and comparable body exposure was observed in both healthy subjects and acute renal failure patients. The extent of LZD exposure was significantly increased by 3-fold in ESRD patients in their off-dialysis day. Furthermore, the $t_{1/2}$ and *MRT* values were significantly increased by ~5- and 3-fold, respectively. The V_d/F values of LZD did not change with renal function. A significant decrease in CL/F by ~3-fold was observed in ESRD patients in their off-dialysis day however, CL/F was significantly increased by ~4-fold during HD. Approximately half of the administered LZD dose was removed during the HD session in these selected cohorts of ESRD patients. LZD was generally well tolerated. *Conclusions:* The dose of LZD did not need to be adjusted for patients with acute renal dysfunction or ESRD on HD. One of the twice-daily doses should be administered after the dialysis session because almost half of the LZD dose was substantially removed by HD. During the first three dialysis sessions of the treatment course, to avoid potentially ineffective therapy, a supplemental dose of LZD might be given if necessary or the dose of LZD should be administered 4 h before the beginning of the HD session. This was to keep LZD levels above the MIC for the organism causing the infection being treated. Copyright © 2014 John Wiley & Sons, Ltd.

Key words: linezolid; pharmacokinetics; hemodialysis; dosing adjustment

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Introduction

Linezolid (LZD) is the first approved antibacterial drug from the oxazolidinone class. It has a good activity against most Gram-positive bacteria and mycobacteria [1]. It acts uniquely by inhibiting bacterial protein synthesis [1]. Linezolid is dosed intravenously or orally at 400 or 600 mg twice a day. Because the bioavailability of linezolid is approximately 100% [2,3], no dosage adjustment is needed when therapy is changed from the intravenous to the oral route [2]. After oral doses of 600 mg, steady-state peak serum concentrations are reached 0.5–2 h after administration [4–7]. The mean linezolid trough concentration was 4.2 ± 2.1 mg/l [8]. The level of plasma protein binding is 31% and the volume of distribution approximates to the total body water content of 40–50 litres [9,10]. The average half-life ranges from 3.4 to 7.4 h in adults [7,8]. The oxidative metabolism of linezolid is non-enzymatic and does not involve the hepatic microsomal oxidative system CYP450 [6]. Clearance occurs by both renal and non-renal mechanisms [9]. However, excretion in urine was the dominant route of elimination, accounting on average for 83–84% of dose [6]. Linezolid should be used with caution in patients with severe renal insufficiency [6].

Renal failure patients were treated with linezolid for proven or suspected infections by multi-resistant Gram-positive cocci [11]. Dosing changes in hemodialysis (HD) patients might be expected because of accumulation caused by kidney failure and/or because of the procedure used to remove the drug from the circulation. The available data regarding the pharmacokinetics (PKs) of linezolid in patients with renal impairment are rare and contradict each other. For example, according to the manufacturer's prescribing information [10] and the data published by Brier *et al.* 2003 [9], no dosage adjustment is needed in patients with renal dysfunction. Conversely, Slatter *et al.* 2001 [6] reported that linezolid should be used with caution in patients with severe renal insufficiency. Also, Tsuji *et al.* 2008 [12] evidenced that careful monitoring and dose adjustment of linezolid is necessary in hemodialysis patients. The aim of this study was to determine if dose adjustment of linezolid was needed as a function of renal impairment or not, especially because urinary excretion is the dominant route of linezolid elimination [6]. Accordingly, the single dose pharmacokinetics of linezolid was investigated in non-infected Egyptian male subjects with various degrees of renal impairment ranging from normal to severe chronic impairment, including end-stage renal disease (ESRD) patients maintained on hemodialysis. Hemodialysis patients were studied while they were on and off dialysis.

Methods

Subjects

Eighteen non-infected Egyptian male subjects were recruited and assessed for inclusion in the study. The subjects were selected randomly from a database and underwent a standardized screening procedure to confirm their eligibility, 14 days before admission. Eligible subjects were classified into three groups depending on their 24 h urinary creatinine clearance (CL_{cr}) values [9,13] or hemodialysis status. Group 1 included six healthy subjects with normal renal function ($CL_{cr} > 80$ ml/min); Group 2 included six patients with acute renal failure (RF) ($30 < CL_{cr} < 80$ ml/min); and Group 3, six patients on long term HD ($CL_{cr} < 20$ ml/min) (minimum period of dialysis was 40 months while maximum period were 130 months) with an ideal body weight of > 60 kg (calculated as $\{\text{height (cm)} - 100\} \times 0.9$) and a body mass index between 20 and 26 kg/m^2 (calculated as {weight (kg)/height (m^2)}). They were chosen from the inpatients hemodialysis unit at Kobre El Koba Medical Clincal Center, Cairo, Egypt. The demographic characteristics of the study groups are given in Table 1.

All subjects gave their written informed consent to participate in the study after they had been well informed about the study objectives, method and possible risks. After a physical examination, subjects with any abnormality of the cardiovascular, respiratory, abdominal or central nervous system were excluded. Blood pressure (BP) and heart rate (HR) were measured. Additionally, an electrocardiogram was conducted and a general examination of the subject was performed to exclude any illness or abnormality (e.g. anemia, cyanosis, clubbing, jaundice and lymphadenopathy).

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Table 1. Demographic characteristics of the study groups

Characteristic	Group 1 (Healthy subjects) $CL_{cr} > 80$ ml/min	Group 2 (Acute RF subjects) $30 < CL_{cr} < 80$ ml/min	Group 3 (ESRD subjects) $CL_{cr} < 20$ ml/min	Normal range
No. of volunteers	6	6	6	
Age (years)	26.4 ± 5.0 (22–32)	38.2 ± 7.3 (26–45)	43.4 ± 7.5 (30–50)	NA
Body weight (kg)	71.4 ± 5.8 (67–85)	76.8 ± 6.8 (66–87)	73.7 ± 4.2 (70–83)	NA
Height (cm)	178.3 ± 6.8 (167–183.1)	173.8 ± 5.5 (162.2–180)	170.8 ± 4.7 (160.2–188.4)	NA
BMI (kg/m^2)	23.3 ± 2.1 (20.4–26.1)	25.1 ± 3.1 (23.1–27.4)	22.8 ± 4.5 (21.8–28.1)	18–30
Systolic BP (mm Hg)	120.8 ± 2 (115–125)	135.4 ± 6 (125–140)	165.5 ± 20.1 (150–190)	120
Diastolic BP (mm Hg)	77.1 ± 2.8 (75–85)	90 ± 10 (85–110)	117.1 ± 9.8 (95–130)	80
Pulse (/min)	74.9 ± 1 (71–78)	75.5 ± 4.5 (70–80)	74.2 ± 3.6 (71–80)	70–80
Sr_{cr} (mg/dl)	0.78 ± 0.1 (0.6–1.3)	4.1 ± 1 (3.1–4.5)	15.7 ± 0.9 (14.3–16.2)	0.8–1.5
CL_{cr} (ml/min)	93 ± 12 (83–121)	64 ± 18 (52–79)	NA	> 80
ALP (UI)	65.1 ± 7.3 (44–98)	75.2 ± 14.1 (55–124)	80.1 ± 18.3 (59–133)	38–126
Glucose (mg/dl)	85.2 ± 5.5 (80–97)	78.1 ± 6.4 (77–86.5)	81.2 ± 4.5 (80.3–89.1)	60–100
Uremia (mg/dl)	25.3 ± 5.1 (13–41)	50.4 ± 7.4 (30.1–59.3)	85.5 ± 6.2 (70.7–91.8)	0–50
Total cholesterol (mg/dl)	171.7 ± 9.2 (165–210)	162 ± 10.5 (160–180.5)	209.1 ± 11.2 (180.3–212.5)	150–250
Triglyceride (mg/dl)	95.3 ± 14 (70–140)	122.4 ± 16.1 (119.1–140.2)	181.2 ± 22.3 (179.1–230.3)	60–165
Uric acid (mg/dl)	4.4 ± 1 (3.3–6.7)	5.2 ± 2.3 (3.5–6.9)	5.6 ± 3 (4–8)	Up to 7
AST (UI)	31.3 ± 4.6 (9–39)	32.3 ± 5.4 (8–37)	29.8 ± 8.1 (9–35)	5–40
ALT (UI)	21.3 ± 7.1 (8–39)	25.6 ± 7.2 (11–40)	24.2 ± 6.4 (10–39)	7–56
Hematocrit (%)	48.5 ± 4.1 (40.1–53.5)	21.7 ± 6.8 (20–33)	16.7 ± 9.1 (15–35)	40–54
Leukocytes (μml)	7741 ± 1101 (5000–8500)	7500 ± 1220 (6000–9100)	8400 ± 1430 (760–9800)	5000–10.000
Hemoglobin (g%)	15.2 ± 0.8 (14.0–16.2)	8 ± 0.9 (9–10)	9.0 ± 3 (8.5–12)	13–16
Total bilirubin (mg/dl)	0.6 ± 4.3 (0.3–1.1)	0.5 ± 1.2 (0.4–1.3)	0.4 ± 1.6 (0.3–1.3)	0.2–1.3

Data represented as mean ± SD (range).

BMI, body mass index; BP, blood pressure; S_{cr}, serum creatinine; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CL_{cr}, creatinine clearance; NA, not applicable; SD, standard deviation.

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Blood samples (10 ml) were collected for a complete blood count, BUN and electrolytes, liver function tests, renal function tests and random blood glucose. Serologic tests were conducted for the presence of hepatitis B surface antigen, hepatitis C virus antibody and HIV antibodies. Urine samples (in the case of Groups 1 and 2) were also collected for microscopic examination analysis. Subjects were admitted to the study after a review of pathology reports, medical history and making sure they met all the study inclusion and exclusion criteria. Upon completion of the study, the physical examination and clinical laboratory measurements were repeated. Blood samples were drawn from each volunteer at study end for assessment of all laboratory parameters as mentioned before, except for the serologic tests, which were not tested again.

The subjects were instructed to abstain from taking any medication for at least 14 days prior to and during the study period. They were also prohibited from consuming caffeinated beverages within 3 days prior to drug administration and until completion of the study. Subjects were excluded from the study if they had a history of clinically significant organ dysfunction other than renal disease or those diseases associated with renal disease (as in the case of Groups 2 and 3) or if they had physical examination or laboratory test results outside the inclusion, such as sitting systolic BP (SBP) of >140 or <100 mm Hg, diastolic BP (DBP) >90 or <60 mm Hg (as in the case of Groups 1 and 2), or a pulse rate of >95 or <50 beats/min at screening; history of orthostatic hypotension; history of serious intolerance, allergy or sensitivity to linezolid; history of blood dyscrasias; history of alcohol, smoking or drug abuse; donation of blood during the 8 weeks prior to the study or plans to donate blood during or within 8 weeks of completing the study; unable to tolerate vein puncture and multiple blood samplings; any surgical or medical condition that might alter the absorption, distribution, metabolism, excretion of linezolid; or could not follow instructions, according to the investigator's opinion.

Study design

This study was carried out in accordance with the International Conference of Harmonization (ICH) guidance on general considerations for clinical trials [14]. The dose of linezolid used in this study was selected based on the minimum daily dosage regimen of linezolid (600 mg) according to the terms of safety and therapeutic efficacy. The pharmacokinetics of linezolid were determined following the administration of a single oral dose of 600 mg of linezolid (Zyvox® tablets, Pharmacia & Upjohn a Division of Pfizer New York, USA). An open-label, parallel-group design was used to evaluate the pharmacokinetics of linezolid in the selected subjects after an overnight fast of at least 12 h. The subjects were non-infected male subjects with various degrees of renal impairment including healthy (Group 1), acute RF patients (Group 2) and dialysis-dependent ESRD patients (Group 3) in their on- and off-dialysis day. Group 3 patients were randomly studied twice with a 2 week washout period between treatments; the first one during an inter-dialytic period (off-dialysis) and the other during an intra-dialytic period (on-dialysis).

The ESRD patients had been treated with injectable erythropoietin (Eprix®) and iron supplementation as essential treatment for anemia, also phosphate binding drugs (e.g. calcium acetate) as a treatment for osteoporosis. Additional therapy consisting of active vitamin D and water soluble vitamins was also administered. All chronic hemodialysis patients received a variety of antihypertensive treatments such as atenolol, captopril, indopamide hemihydrates, methyldopa, amlodipine besylate, isosorbide 5-mononitrate, perindopril tert butyl amine and diltiazem. No patient received antacid to avoid any potential drug–drug interactions.

In the week before receiving the study medication, the subjects underwent a physical examination and laboratory tests in order to ensure that all subjects met the inclusion and exclusion criteria. For Groups 1 and 2, a 24 h urine collection was obtained for determination of CL_{cr}. The results of the 24 h CL_{cr} were compared with an estimate of CL_{cr} by use of the equation of Cockcroft and Gault [15], where CL_{cr} (ml/min) = [(140 − age) * TBW] /72 * Scr.

On the day prior to the study, the subjects were hospitalized. They received a single oral dose of 600 mg linezolid followed by 240 ml of water after overnight fasting. Subjects continued fasting for another 2 h after drug administration. They remained in the clinical research unit until 48 h

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after dosing in the case of Groups 1 and 2 and until 72 h after dosing in the case of Group 3. They received standardized meals 2, 6 and 12 h after drug administration with avoidance of excess fat or tyramine containing foods (such as pork, aged cheeses, alcoholic beverages, or smoked and pickled foods), in addition to beverages such as coffee, tea and cola. This is because linezolid is a weak monoamine oxidase inhibitor (MAOI), and should not be used concomitantly with other MAOIs (such as paroxetine and sertraline), large amounts of tyramine-rich foods or serotonergic drugs to avoid serotonin syndrome [16]. All dietary, smoking and drug/herbal product restrictions were maintained throughout the study period. After discharge, the physical examination and clinical laboratory measurements were repeated for the assessment of tolerability.

For Group 3 patients receiving long term thrice-weekly hemodialysis, they were studied twice: once on their dialysis day and between dialysis sessions. The dialysis treatment time, blood flow rate, dialysate flow rate and ultra-filtration rate were the same as those normally prescribed to maintain adequate hemodialysis for each patient and were not changed for the purpose of this study. The durationof standard dialysis ranged from 3.0 to 4.5 h (mean 3.5 ± 0.5 h) using a Fresenius Medical Care (Fresenius, 2010 F10; Bad Hamburg, Germany). Dialysers and lines were steam sterilized, and no patient had dialyser reuse. The blood flow rate was 220 ml/min and the dialysate flow rate was 500 ml/min. The hematocrit was determined for each of the arterial blood samples. All patients had bicarbonate dialysis and anticoagulation with low molecular weight heparin. The amount of dialysate processed was recorded.

Sample collection

For the pharmacokinetic assessments, blood samples (5 ml) were collected from an indwelling intravenous catheter inserted into the antecubital vein of the forearm of each subject prior to drug administration (blank), then at 0.5, 1.0, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36 and 48 h after drug administration in heparinized tubes. Additional blood samples were obtained at 72 h for patients in Group 3 in their off-dialysis day. For patients in Group 3 during hemodialysis, oral 600 mg linezolid was given 1.5 h before the beginning of dialysis and simultaneous blood sample were collected from venous access ports of the hemodialysers (dialyser outlet) immediately prior to the hemodialysis session and 30 min after the beginning, then hourly thereafter, until the end of the treatment session (4 h). The blood samples were centrifuged and the plasma was harvested and transferred to polystyrene microcentrifuge tubes and stored at −80 °C until assay for linezolid using a validated high-performance liquid chromatography (HPLC) method [7].

Bioanalytic assessments

The plasma level of linezolid was measured using a validated HPLC-UV method [7]. Briefly, the mobile phase comprised 20 mM ammonium phosphate buffer (pH = 3) and acetonitrile solution (72:28, v/v). The elution was isocratic at ambient temperature with a flow rate of 1.5 ml/min. The separation was achieved using a LiChrospher®100 RP-18 column (250 × 4 mm, 5 μm; Merck KGaA, Darmstadt, Germany). The effluent was monitored using a Shimadzu SPD-10AVP UV–VIS detector at 254 nm for linezolid and the internal standard (tinidazole), and peak areas were integrated and calculated electronically using the Class-VP data analysis program (all Shimadzu Scientific Instruments, Kyoto, Japan). The calibration curves include all drug concentrations measured in clinical practice with within-day and between-day accuracies and precision were in accordance with FDA guidelines [17]. Calibration curves (n = 10) were found to be linear over the entire concentration range of linezolid (0.05–50 μg/ml), with a correlation coefficient $R^2 > 0.999$ throughout the course of the assay for linezolid. The lower limit of quantification (LLOQ) and the limit of detection (LOD) were 0.05 and 0.01 μg/ml, respectively. The within-day and between-day coefficients of variance (%CV) were always within ± 12% in the entire range of the calibration curve (0.05–50 μg/ml).The within-day accuracy ranged between 99.8% and 105.1%, whereas the between-day accuracy ranged between 98.3% and 106.9%. The concentrations of the quality control samples were 40, 25 and 0.15 μg/ml, respectively. The absence of interference of linezolid with tinidazole was verified.

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Pharmacokinetic analysis

Individual plasma concentration–time profiles of linezolid were analysed according to non-compartmental and compartmental analysis. A non-compartmental PK analysis was calculated with an Excel spreadsheet (Microsoft, 2007). The elimination rate constant (k) was estimated by least squares regression of plasma concentration-time data points in the terminal log-linear region of the curves. The half-life ($t_{1/2}$) was calculated as 0.693 divided by k. The AUC from zero to the last measurable plasma concentration ($AUC_{0\text{-}t}$) was calculated using the linear trapezoidal rule. The AUC from zero to infinity ($AUC_{0\text{-}\infty}$) was calculated as $AUC_{0\text{-}\infty}$ ($AUC_{0\text{-}t} + C / k$), where C is the last measured concentration [18,19]. C_{max} and t_{max} were directly obtained from the individual plasma concentration–time curve. The apparent total clearance (CL/F) was calculated as Dose/$AUC_{0\text{-}\infty}$. While the apparent volume of distribution (V_d/F) was estimated as Oral clearance/k relative to the bioavailability (F) of linezolid. The area under the first moment curve ($AUMC$) was calculated by trapezoidal integration and extrapolation to infinity. The mean residence time (MRT) was calculated as the ratio ($AUMC$)/($AUC_{0\text{-}\infty}$) [18,19].

A two-compartment open pharmacokinetic model with first-order absorption and first-order elimination with or without lag time was utilized to describe the plasma concentration–time profile of linezolid after oral administration. The elimination rate and clearance were represented by K_e and CL. The corresponding rate constant was expressed as K_{12} and K_{21}, respectively. The rate of distribution phase and elimination phase was represented by α and β, whereas the corresponding half-life was expressed as $T_{1/2,\alpha}$ and $T_{1/2,\beta}$ [18,19]. The plasma data were modeled using WinNonlin version 2.0 pharmacokinetic software (Pharsight Corporation, 1994–1998, Palo Alto, CA) to calculate the previous data.

To study the dialysability of linezolid, the percentage of the extraction fraction (EF%) during hemodialysis was calculated. The plasma linezolid levels were determined during the 4 h period of hemodialysis for ESRD patients (Group 3). The blood samples were taken after 1.5 h from drug administration. The EF% was calculated as $(C_{beg} - C_{end})/C_{beg} \times 100$. Where C_{beg} is the linezolid plasma concentration immediately after the beginning of the dialytic period; C_{end} is the linezolid plasma concentration at the end of the dialytic period.

Statistical analysis

The pharmacokinetic parameters were calculated and the results are presented as the mean ± coefficient of variation (%CV). Statistical comparisons between groups were made with Student's t-test. The AUC, C_{max} and CL/F values were evaluated after logarithmic transformation according to the USP guidelines [20], providing point estimates and 90% confidential intervals (CI) [21] for the T/R ratio. All statistical analyses were performed using the Excel spreadsheet on an IBM PC (Microsoft, 2007). A value of $p \leq 0.05$ and 90% CI falling outside the specified limit of 80% to 125%, was taken as the level of significance.

Results

The study enrolled 18 subjects; all of them completed the study. Safety profiles and pharmacokinetic characteristics were assessed in all subjects who completed the study. The demographic characters are presented in Table 1. In the present study, measures were taken to protect the safety of the subjects, including prolonging the time of lying in bed and remaining in the clinical research unit, and enhancing the clinical monitoring and nursing. All subjects were negative for hepatitis and HIV. None of the 18 subjects had an anamnestic known hypersensitivity to linezolid or the oxazolidinone class.

Patients had received maintenance hemodialysis, the period of dialysis was 96.2 ± 37.1 months. They had no acute undercurrent illness, and their post-dialysis body weight was within 10% of their ideal body weight. Etiologies of renal failure are hepatorenal syndrome, sepsis with multiple organ dysfunction syndrome (MODS), ischemic acute tubular necrosis (ATN), idiopathic ATN, idiopathic thrombocytopenia purpura, ATN sepsis with MODS and ATN unknown etiology. None of subjects had been administered a linezolid bacteriostatic drug before the study.

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Safety and tolerability

None of the enrolled subjects showed any signs of serious adverse drug reactions (ADRs) during or after completion of the study. Linezolid was well tolerated in the participating subjects. The most commonly reported ADRs associated with linezolid administration were dizziness (one report), headache (two reports) and diarrhea (one report), which are well-known ADRs associated with linezolid. Physical examination, electrocardiograms and laboratory tests revealed no clinically significant changes.

Pharmacokinetic evaluation

The mean linear and semi logarithmic plasma concentration–time curve of linezolid administered orally on different occasions as a single dose are represented in Figure 1. The average non-compartmental and compartmental pharmacokinetic parameters of linezolid are summarized in Table 2. For the end stage renal disease patients, the pharmacokinetic parameters of linezolid determined during hemodialysis are illustrated in Table 3 including statistical analysis with pharmacokinetic parameters in their day off-dialysis. The mean plasma levels during hemodialysis in comparison with the mean plasma levels in day off-dialysis are illustrated in Figure 2.

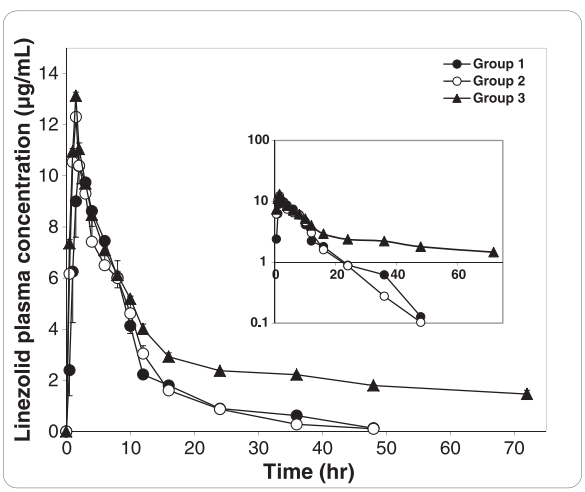

Figure 1. Mean linear and semilogarithmic linezolid plasma concentration–time profiles after oral administration of 600 mg dose to volunteers, by group; Group 1 ($CL_{cr} > 80$ ml/min), Group 2 ($30 < CL_{cr} < 80$ ml/min), Group 3 (ESRD patients)

The removal of linezolid from the central compartment to the peripheral compartment and the transport between the central compartment and the peripheral compartment were all consistent with first-order kinetics. Linezolid was absorbed rapidly and was eliminated bi-exponentially after oral administration to the investigated groups (Figure 1). A low inter-subject variability in C_{max} (%CV ranged from 2.8% to 14.1%) and *AUC* (%CV of 5.4–16.8%) was observed (Table 2). The plasma concentration–time profiles showed comparable linezolid profiles in the case of Groups 1 and 2, indicating a similar rate and extent of absorption and elimination and comparable body exposure between healthy subjects and acute renal failure patients (Figure 1 and Table 2). Conversely, oral administration of linezolid to Group 3 in the day off-dialysis significantly increased the $AUC_{0\text{-}\infty}$ (3-fold) and the C_{max} (~11%) of linezolid compared with Groups 1 and 2.

The rate of linezolid absorption was the same after oral administration to all subjects (Table 2). The peak plasma concentration was reached 1. 5–2 h after oral administration of linezolid. Likewise, the V_d/F values of linezolid did not change with renal function and ranged from 46.3–48.8 litres in the three groups (Table 2). The CL/F values of linezolid were similar in healthy and acute renal failure subjects. However, a significant decrease in CL/F by approximately 3-fold was observed in the ESRD patients in their off-dialysis day. Furthermore, the $t_{1/2}$ and *MRT* values were significantly increased by approximately 5- and 3-fold, respectively, in ESRD patients in their off-dialysis day compared with Groups 1 and 2 (Figure 1 and Table 2). From the compartmental analysis, a significant increase in the $t_{1/2}$ of β of off-dialysis ESRD patients was observed which coincided with the increased value of $t_{1/2}$ calculated by the non-compartmental analysis (Table 2).

Six ESRD patients were dialysed for 4 h and approximately half of the administered linezolid dose (57.1%) was removed during the dialysis session (Table 3). All the calculated pharmacokinetic parameters represented in Table 3 were changed during hemodialysis, except C_{max}. The $AUC_{0\text{-}\infty}$, $t_{1/2}$, *MRT* and V_d/F values were significantly decreased during hemodialysis compared with their off-dialysis day (Table 3). Approximately 4-fold decreases in $t_{1/2}$ and $AUC_{0\text{-}\infty}$ and 2-fold

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Table 2. Pharmacokinetics (PKs) of linezolid in patients with different renal impairments after a single oral dose administration of a 600 mg linezolid

PK variable	Group 1 (Healthy subjects) (CLcr >80 ml/min)	Group 2 (Acute RF subjects) (30 < CLcr < 80 ml/min)	Geometric mean (90% CI)	Group 3 (ESRD subjects) (CLcr < 20 ml/min)	Geometric mean (90% CI)
Non-compartmental PK					
C_{min} (μg/ml)	0.12 (12.3)	0.11 (9.9)		1.45 (23.1)	
C_{max} (μg/ml)	11.8 (14.1)	12.3 (3.4)	0.953 (0.900–1.010)	13.2 (2.8)[a,b]	1.102 (0.983–1.237)
t_{max}[†] (h)	2.0 (1–4)	1.5 (1.5–2)		1.5 (1.5–1.5)	
$AUC_{0\to t}$ (μg.h/ml)	108.7 (9.2)	108.4 (16.8)	0.971 (0.856–1.101)	213.0 (5.4)[a,b]	1.929 (1.851–2.010)
$AUC_{0\to\infty}$ (μg.h/ml)	110.1 (9.2)	111.4 (16.0)	1.021 (0.937–1.113)	324.6 (10.2)[a,b]	2.996 (2.825–3.177)
$t_{½}$ (h)	7.5 (9.5)	7.5 (4.6)		34.5 (16.0)[a,b]	
MRT (h)	9.0 (11.0)	8.59 (4.5)		25.2 (16.6)[a,b]	
CL/F (ml/min)	91.9 (17.5)	91.1 (17.0)	0.969 (0.827–1.135)	31.0 (10.3)[a,b]	0.330 (0.315–0.345)
V_d/F (l)	48.8 (9.7)	47.3 (16.7)		46.3 (7.4)	
Compartmental PK					
$AUC_{0\to\infty}$ (μg.h/ml)	100.8 (13.5)	112.8 (19.3)	1.019 (0.914–1.136)	343.7 (22.0)[a,b]	3.042 (2.697–3.432)
Ka (h^{-1})	1.16 (29.1)	1.0 (11.1)		1.54 (24.4)	
K_{12} (h^{-1})	0.43 (77.1)	0.34 (37.7)		0.17 (79.0)	
K_{21} (h^{-1})	1.02 (61.7)	0.57 (46.6)		0.07 (81.6)	
β (h^{-1})	0.18 (43.0)	0.1 (18.6)		0.02 (71.1)	
$t_{½}$ of β (h)	6.8 (31.0)	7.1 (20.1)		44.3 (38.0)[a,b]	
α (h^{-1})	1.5 (52.4)	1.02 (10.1)		0.29 (78.7)	
$t_{½}$ of α (h)	0.64 (74.3)	0.68 (10.8)		3.1 (35.9)	
CL/F (ml/min)	100.7 (12.7)	91.6 (20.9)	0.951 (0.838–1.093)	31.2 (19.3)[a,b]	0.318 (0.273–0.371)
EF (%)				57.1 (7.5)	

Values are presented as the arithmetic mean (coefficient of variation).
[a]Significantly different from Group 1 at $p < 0.05$ and
[b]Significantly different from Group 2 at $p < 0.05$.
[†]Median (minimum to maximum).
ESRD, end stage renal disease; RF, renal failure; C_{max}, peak plasma concentration; t_{max}, time to reach peak plasma concentration; $AUC_{0\text{-}\infty}$, area under the concentration-time curve from zero to infinity; $AUC_{0\text{-}t}$, area under the concentration-time curve from zero to the last measurable plasma concentration; $AUC_{t\text{-}\infty}$, area under the concentration–time curve from the last measurable plasma concentration to infinity; $t_{1/2}$, elimination half-life; MRT, mean residence time; CL/F, clearance; CLcr, creatinine clearance; V_d/F, volume of distribution; k_a, absorption rate constant; α and β, hybrid disposition rate constant; $t_{½}$ of β, elimination half-life; k_{21}, redistribution rate constant from the peripheral to the central compartment; k_{12}, redistribution rate constant from the central to the peripheral compartment; EF, extraction fraction during hemodialysis.

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Table 3. Some pharmacokinetic (PK) parameters determined during hemodialysis and day off-dialysis from plasma levels of linezolid following oral administration of 600 mg linezolid to end stage renal disease patients

	Group 3 (ESRD patients) (CLcr < 20 ml/min)	
PK variable	Off-dialysis	During-dialysis
C_{max} (μg/ml)	13.2 (2.8)	12.9 (3.7)
$AUC_{0\rightarrow\infty}$ (μg.h/ml)	324.6 (10.2)	78.9 (19.8)*
$t_{½}$ (h)	34.5 (16.0)	5.5 (31.1)*
MRT (h)	25.2 (16.6)	2.7 (9.5)*
CL/F (ml/min)	31.0 (10.3)	130.6 (18.7)*
V_d/F (l)	46.3 (7.4)	20.7 (10.1)*
EF (%)		57.1 (7.5)

Values are presented as the arithmetic mean (coefficient of variation).
*Significant difference from day off -dialysis at $p < 0.05$.

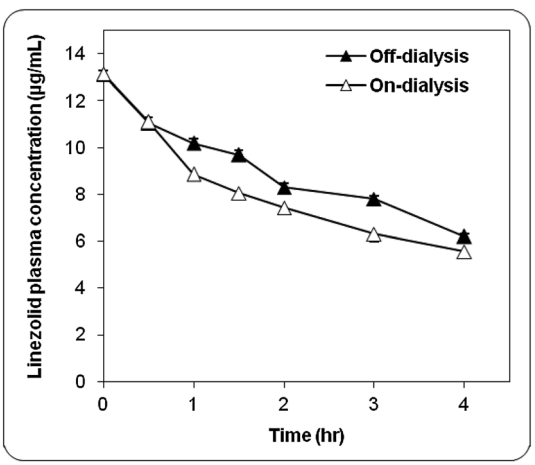

Figure 2. Mean linear linezolid plasma concentration–time profiles after oral administration of 600 mg dose to the end stage renal disease patients (Group 3) on-dialysis (Δ) and off-dialysis (▲)

decreases in V_d/F values were observed during hemodialysis. Conversely, the CL/F was significantly increased from 31.0 ml/min to 130.6 ml/min (~4-fold) during hemodialysis (Table 3).

Discussion

Infections with Gram-positive organisms are highly prevalent in hemodialysis patients and are a major cause of morbidity and mortality in this population. The extensive use of antimicrobial agents in hemodialysis patients has resulted in a growing threat of resistance, especially among Gram-positive bacteria. Vancomycin-resistant enterococci and *S. aureus* isolates with reduced susceptibility to vancomycin are increasingly being reported as a major cause of infection in hemodialysis patients [22,23].

Linezolid is an effective treatment option for serious infections caused by drug-resistant Gram-positive bacteria [22,23]. Dosing adjustment in hemodialysis patients might be expected because of accumulation caused by kidney failure and/or the procedure used for drug removal from the circulation. Drug removal during dialysis could be affected by either drug-related or procedure-related factors [24]. Drug-related factors such as molecular weight, water solubility, protein binding and V_d. Procedure-related factors such as type of dialyser, blood flow rate, duration of dialysis session and dialysate flow rate. Accordingly, the appropriate use of an antibiotic against vancomycin-resistant organisms in patients with impaired renal function especially ESRD patients requires detailed knowledge of the disposition and pharmacokinetics of linezolid in individuals who may have decreased drug clearance and the effects of dialysis on drug or metabolite removal.

The pharmacokinetics of linezolid in healthy subjects and in acute RF and ESRD patients maintained on dialysis were studied. The pharmacokinetics of linezolid in healthy subjects (Group 1) and acute RF patients (Group 2) were in good agreement with the finding of previous investigations, which emphasizes the validity of the present results [6,7,9]. Following the oral administration of 600 mg linezolid, the plasma concentration rapidly reached a peak concentration, and then decreased slowly reaching the last measurable plasma concentration of 0.1 μg/ml after 48 h in the case of Groups 1 and 2 and 1.45 μg/ml after 72 h (considering that ESRD patient were dialysed at 48 h after dosing) in the case of Group 3. The concentration–time course of linezolid was not changed in Groups 1 or 2. The only noticeable effect was a slight increase in the C_{max} (~1%) in acute RF patients, however, this finding was unlikely to have any clinical significance.

Significant differences in the linezolid pharmacokinetics were evident in ESRD patients compared with healthy subjects. In the case of ESRD

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patients in the day off-dialysis, a significant increase in C_{max}, $AUC_{0-\infty}$, $t_{1/2}$ and *MRT* could be attributed to the accumulation caused by kidney failure, resulting in a longer duration of the linezolid antimicrobial effect in their day off-dialysis. The V_d/F was not affected by renal function, which was in good agreement with those published earlier [9]. Conversely, subjects with ESRD were anuric and exhibited a much reduced mean CL/F compared with healthy and acute RF subjects. The CL/F of linezolid was reduced by ~60%, leading to a dramatically longer half-life and increased exposure in ESRD subjects in the day off-dialysis (Table 2). During hemodialysis, the *AUC* of linezolid was significantly decreased in comparison with the day off-dialysis, because a significant portion would be removed during the hemodialysis session. This finding was in good agreement with the previously published data [9]. Accordingly, the previous observation reflected a strong relationship between the renal clearance of the drug and CL_{cr}. As a result, renal function had an effect on the overall clearance of the drug.

In fact, a few reports investigated the contribution of renal function to the pharmacokinetics of linezolid, however, their results were controversial [9,25,26]. Sasaki *et al*. 2011, showed a significant contribution of renal function to the total clearance [25]. On the other hand, Brier *et al*. 2003 reported that renal function had little effect on the overall clearance of the drug and the observed increase in the non-renal clearance was due to a decrease in CL_{cr}. They explained this apparent compensatory increase in non-renal linezolid clearance by enhanced drug biotransformation, biliary excretion, decreased absolute bioavailability or changes in drug distribution [9]. Also, Meagher *et al*. 2003 investigated the pharmacokinetics of linezolid in infectious patients with a population approach and suggested a minor contribution by renal elimination, with CL_{Cr} explaining 16% of the total variance in the linezolid clearance [26]. They reported that the increase in linezolid concentrations resulted in the saturation of the non-renal clearance pathway in patients with reduced renal clearance. This might explain the discrepancy in the contribution of renal function to linezolid clearance among the studies. Accordingly, further study is warranted to elucidate the contribution of renal and non-renal clearance pathways on the overall clearance of linezolid. At physiological pH, linezolid exists in an uncharged state. It is a moderately water-soluble molecule (approximately 3 mg/ml), with a log*P* of 0.55 [27]. Besides, the low level of plasma protein binding is 31% and a high V_d which approximates to the total body water content of 40–50 litres [10]. All these factors support the dialysability of linezolid.

Despite the high molecular weight of linezolid (337.45 g/mol), it could be removed during hemodialysis especially with high-flux membranes. As linezolid is a dialysable drug, a significant portion of the dose could potentially be removed during a hemodialysis session, depending on the time of administration of the last dose in relation to the time of the hemodialysis session [9]. The *EF*% is useful in comparison between some pharmacokinetic parameters of drugs such as intra-dialytic plasma $t_{1/2}$ and hemodialysis clearance using a different dialyser membrane [28]. Accordingly, it is considered as a guide to determine the dialysability of the drugs, the molecular weight and the efficiency of the dialyser membrane. Approximately half of the administered linezolid dose (57.1%) was removed during the dialysis session. This was attributed to the dialysability of linezolid. A typical hemodialysis session occured at a frequency of three times per week, with 48 to 72 h between the start sessions [9]. Therefore, a potential for the elimination of a significant portion of the linezolid dose could be predicted in one of every four to six doses [9].

Accumulation of linezolid metabolites could be strongly expected in patients with renal impairment, especially those with ESRD. This was evidenced by the large increase in $AUC_{0-\infty}$ of ESRD patients in their off-dialysis day. This is because the two linezolid metabolites are almost exclusively eliminated in urine [6]. The clinical significance of the accumulation of linezolid metabolites is not fully elucidated and requires additional investigations with single and multiple doses. Hemodialysis with a high efficiency dialysis membrane is considered as a significant source of elimination of linezolid and its two major metabolites in patients with ESRD. Approximately more than half of the administered dose of the drug was removed when dialysis was started 1.5 h following the dose administration. This result

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coincides to a large extent with earlier data [9]. The amounts removed depended on the proximity of the dialysis session in time to the time of the dose administration.

A typical dialysis schedule of three times weekly might lead to an average weekly clearance of 90–100 ml/min, which is approximately the average for the other renal function groups (Table 1). The dose of linezolid did not need to be altered for patients with impaired kidney function. In people requiring hemodialysis, care should be taken to give linezolid after a session, because dialysis removed ~50% of the linezolid dose from the body. However, it will be necessary to study the pharmacokinetics of linezolid in a larger number of hemodialysis patients to confirm our results.

Conclusion

Despite linezolid elimination being affected by renal function, no dosage adjustment was required for patients with renal impairment. One of the twice-daily doses should be administered after the dialysis session because almost half of the linezolid dose was substantially removed by hemodialysis. During the first three dialysis sessions of the treatment course, to avoid potentially ineffective therapy, a supplemental dose of linezolid might be given if necessary or the linezolid dose should be administered 4 h before the beginning of the hemodialysis session. This was to keep linezolid levels above the MIC for the organism causing the infection being treated.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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