

Pharmacokinetics and Bioequivalence Comparison of 600 mg Single-Dose Linezolid Oral Suspension and Tablet Formulation in Healthy Chinese Subjects

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Abstract

Study background: Linezolid is indicated for the treatment of infections caused by aerobic Gram-positive bacteria. An oral suspension formulation poses an alternative to solid oral formulations in patients with swallowing difficulties, especially pediatric and geriatric patients, or patients with feeding tubes.

Methods: This randomized, open-label, two-way cross-over, clinical pharmacology study in healthy Chinese male subjects evaluated the bioequivalence of single-dose 600 mg linezolid oral suspension to single-dose 600 mg linezolid film-coated tablet under fasted conditions. Pharmacokinetic blood sampling was carried out at various time points within 48 h post-dosing and plasma samples were analyzed using a validated high-performance liquid chromatography tandem mass spectrometric method. The primary endpoints were area under plasma concentration–time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{last}) and maximum plasma concentration (C_{max}) for linezolid.

Results: All 20 enrolled male subjects completed the study (mean age 25 years, mean body mass index 22 kg/m²). The 90% confidence intervals (CIs) for the ratios of the adjusted geometric means of the primary endpoints, AUC_{last} (97.81% [90% CI, 93.11-102.75%]) and C_{max} (113.67% [90% CI, 105.26-122.75%]), for the oral suspension formulation compared with the oral tablet were fully within the established bioequivalence limits of 80-125%. The two linezolid formulations were well tolerated and no serious adverse event or other significant adverse event was noted.

Conclusions: Based on the results of this study, linezolid 600 mg oral suspension and linezolid 600 mg tablets are anticipated to be therapeutically equivalent and could be switched in subjects without any need for dose modification. Both formulations were safe and well tolerated.

Keywords: Linezolid; Pharmacokinetics, Oral suspension; Bioequivalence; Healthy chinese subjects

Abbreviations: AE: Adverse Event; AUC: Area under Plasma Concentration–time Curve; AUC_{inf}: Area under Plasma Concentration–time Curve from Time Zero Extrapolated to Infinite Time; AUC_{last}: Area under Plasma Concentration–time Curve from Time Zero to the Time of the Last Quantifiable Concentration; BMI: Body Mass Index; CI: Confidence Interval; C_{max}: Maximum Plasma Concentration; CRU: Clinical Research Unit; CYP: Cytochrome P450; ECG: Electrocardiogram; HPLC-MS/MS: High-performance Liquid Chromatography Tandem Mass Spectrometry; LLOQ: Lower Limit of Quantification; PD: Pharmacodynamics; PK: Pharmacokinetic; SD: Standard Deviation; t_{1/2}: Elimination Half-life; T_{max}: Time for Maximum Plasma Concentration

Introduction

Linezolid is a synthetic antibacterial agent from the oxazolidinone class of antibiotics that selectively inhibits bacterial protein synthesis [1-4]. Through a unique mechanism of action, linezolid prevents the formation of an essential component of the bacterial translation process that involves binding to a site on the bacterial 23S ribosomal ribonucleic acid of the 50S subunit and inhibiting the assembly of a functional 70S initiation complex [1]. Cross-resistance between linezolid and other classes of antibiotics is unlikely [5,6].

Linezolid is approved for the treatment of infections caused by aerobic Gram-positive bacteria, such as nosocomial pneumonia; community-acquired pneumonia; complicated skin and skin structure

infections, including diabetic foot infections, without concomitant osteomyelitis; uncomplicated skin and skin structure infections; and vancomycin-resistant *Enterococcus faecium* infections. Linezolid is available in three formulations: intravenous solution, oral film-coated tablet, and oral suspension [7]. The usual oral doses of linezolid are 10 mg/kg every 8 or 12 h for pediatric patients (<12 years of age) and 400 mg or 600 mg every 12 h for adults and adolescents (≥ 12 years)[7].

The pharmacokinetics (PK)/pharmacodynamics (PD), efficacy, and tolerability of linezolid have been extensively studied in different Western subpopulations (including men/women, children/adults, young/elderly, healthy volunteers/obese, those with mild/severe renal impairment, and the critically ill) [8-16]. Following oral dosing, peak plasma concentrations are reached after approximately 1 to 2 h and the absolute bioavailability is approximately 100% [8-10,17-20].

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Studies have shown no significant differences in area under the plasma concentration–time profile (AUC) values following administration in the fed or fasted state [17,18,21]. Steady-state volume of distribution is limited to the total body water content of 30 to 50 liters [11]. Plasma protein binding is concentration-independent and approximately 31% [11]. Linezolid is primarily metabolized by oxidation of the morpholine ring to form two inactive ring-opened carboxylic acid metabolites. In vitro studies have demonstrated that linezolid is minimally metabolized and may be mediated by human cytochrome P450 (CYP). However, the metabolic pathway of linezolid is not fully understood. About 30% of the administered dose is eliminated unchanged in the urine, and the low renal clearance (averaged about 40 mL/min) suggests net tubular reabsorption. The mean elimination half-life ($t_{1/2}$) of linezolid is 4 to 7 h in adults [8-10,17,18,20]. Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents [7].

Oral tablet formulation of medication can be problematic for those who have difficulty swallowing solid oral dosage forms, especially pediatric patients, geriatric patients, or patients with feeding tubes, and the oral suspension formulation offers an alternative means of providing medications to such patients. Although a linezolid oral tablet formulation is available in China [22], information on the bioavailability and PK properties of linezolid in the Chinese population are scarce. This article reports the data from a PK study conducted in China to evaluate the bioavailability of single-dose oral suspension of linezolid relative to the reference oral film-coated tablet at 600 mg to obtain registration approval of the oral suspension.

Methods

Study design

This was a randomized, open-label, two-way cross-over, single-dose study conducted in a single site in China (Institute of Antibiotics, Hua Shan Hospital Affiliated to Fudan University, Shanghai, China; www.clinicaltrials.gov identifier: NCT01055769) from March to April 2010. The aim was to establish bioequivalence (primary objective) of single-dose linezolid oral suspension (Zyvox[®], Pfizer Inc., New York, NY, US; lot #09-079488) to single-dose linezolid tablet (Zyvox[®], Pfizer Inc., New York, NY, US; lot #10-081676) and to evaluate the safety and tolerability (secondary objective) of single-dose linezolid oral suspension and single-dose linezolid tablet in healthy Chinese male subjects under fasted conditions.

The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All local regulatory requirements were followed; in particular, those affording greater protection to the safety of study participants. The final protocol, any amendments, and informed consent documentation were reviewed and approved by the Independent Ethics Committee at the investigational center participating in the study (Hua Shan Hospital Affiliated to Fudan University, Shanghai, China).

Study participants

Eligible subjects were healthy males aged 18 to 40 years (as per Chinese regulatory guidance for bioequivalence studies [23]) with a body mass index (BMI) of 19.0 to 24.0 kg/m² and a total body weight >50 kg (110 lbs), who provided informed consent and were willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures. Subjects were deemed healthy if

there were no clinically-relevant abnormalities identified by a detailed medical history, full physical examination (including blood pressure and pulse rate measurement), 12-lead electrocardiogram (ECG), or clinical laboratory tests.

Subjects with any evidence or history of clinically significant disease, allergy or abnormality, positive hepatitis B surface antigen, anti-hepatitis C virus antibody or HIV serology results, with a history of excess consumption of alcohol or tobacco, with any condition possibly affecting drug absorption (e.g., gastrectomy) or who had consumed grapefruit or grapefruit-containing products within 7 days of first study drug dose, who were taking any medicinal product inhibiting monoamine oxidase A or B, strong CYP inducers, sympathomimetic agents, vasopressive agents, or dopaminergic agents within the 2 weeks prior to first study drug dosing, or who had received treatment with an investigational drug within 90 days or five half-lives, whichever is longer, prior to first study drug dosing, were excluded from the study.

Screening assessments occurred within 28 days prior to the first dose of study drug in the first treatment period. Subjects were admitted to the Clinical Research Unit (CRU) the day before dosing and were required to remain at the CRU for intensive PK sampling during each period. Subjects were required to abstain from alcohol, caffeine-containing products, and smoking at least 48 hr prior to the dose of study medication and during the two treatment periods in-house.

Study treatments

Enrolled subjects were assigned to receive each of the following two treatments in random order according to a computer-generated randomization schedule: a single dose linezolid oral suspension 600 mg (30 mL; Test treatment) administered using a syringe with 210 mL of water (in a total of 240 mL of water) under fasted conditions, or a single dose linezolid 600 mg film-coated oral tablet (Reference treatment) administered whole (without chewing) with 240 mL water under fasted conditions. The washout period between the two treatments periods was at least 4 days. Subjects were required to fast overnight (for a minimum of 10 h pre-dose) and for 4 h post-dose. Study drug was administered in the morning after an overnight fast during each treatment period. In order to standardize the conditions on PK sampling days, all subjects were required to refrain from lying down (except when required for blood pressure, pulse rate, and ECG measurements), eating, and drinking beverages during the first 4 h after dosing. Water was permitted until 1 h prior to, and 2 h after, study medication administration.

Pharmacokinetic evaluation

In each period, blood samples (5 mL) were collected in vacutainer tubes containing tripotassium ethylene diaminetetra acetic acid at the following time-points: pre-dose, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h post-dose. After sample collection, plasma specimens were separated from whole blood by centrifugation at approximately 1700×g for 10 mins at 4°C, transferred to polypropylene tubes, and stored frozen at approximately -20°C within 1 h of collection until assayed within the established sample storage stability window as per data generated during method validation.

Plasma samples were analyzed for linezolid concentrations at WuXi AppTec (Shanghai, China) using a validated high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) method. Calibration standard responses were linear over the range of 20.0 to 10,000 ng/mL; using a weighted (1/concentration²) linear regression. Those samples with concentrations above the upper limits

of quantification were adequately diluted into calibration range. The lower limit of quantification (LLOQ) for linezolid was 20.0 ng/mL. The between-day assay accuracy (expressed as percent relative error) of the quality control samples at QC-Low (60.0 ng/mL), QC-Middle 1 (500 ng/mL), QC-Middle 2 (3500 ng/mL), QC-High (8000 ng/mL), and dilution QC (20,000 ng/mL) ranged from 0.5 to 2.0%, and the assay precision (expressed as the between-day percent coefficient of variation [%CV]) was $\leq 4.3\%$.

The PK parameters were AUC from time zero to the time of the last quantifiable concentration (AUC_{last}), AUC from time zero extrapolated to infinite time (AUC_{inf}), maximum plasma concentration (C_{max}), time for maximum plasma concentration (T_{max}), and $t_{1/2}$. Non-compartmental analysis of concentration-time data was used to calculate the PK parameters, employing internal electronic non-compartmental analysis software (eNCA version 2.2.1). AUC was calculated using the linear-log trapezoidal method, C_{max} and T_{max} were reported as observed, and $t_{1/2}$ was calculated as $\ln 2/k_{el}$, where k_{el} is the slope of the log-linear terminal portion of the concentration-time curve. Samples below the LLOQ were set to 0 ng/mL and actual sample collection times were used to conduct the PK analysis.

Safety evaluation

Subject safety was monitored throughout the study by physical examination, ECG, laboratory test results, recording of vital signs, and clinical interview for solicitation of adverse events (AEs).

Statistical analyses

Natural log transformed AUC_{inf} , AUC_{last} , and C_{max} of linezolid (normally distributed data) were analyzed (SAS version 9.2) using a linear mixed-effect model with sequence, period, and treatment as fixed effects and subject within sequence as a random, mixed module procedure. Estimates of the adjusted mean differences (Test treatment-Reference treatment) and corresponding 90% confidence intervals (CIs) were exponentiated to provide estimates of the ratio of adjusted geometric means (Test treatment/Reference treatment) and 90% CIs. Bioequivalence was concluded if the 90% CIs for the ratio of adjusted

geometric means for both AUC_{last} and C_{max} were completely within the boundaries of 80 to 125%. Descriptive statistics were used to summarize the PK parameters, including AUC_{inf} , AUC_{last} , and C_{max} , T_{max} , and $t_{1/2}$.

A sample size of 18 completers (nine subjects per sequence) was planned to provide at least 96% power that the 90% CI for the ratio of Test treatment to Reference treatment for AUC_{last} would lie within the acceptance region of 80 to 125%, and 99% power that 90% CI for the ratio of Test treatment to Reference treatment for C_{max} would lie within the acceptance region of 80 to 125%. Consequently, this sample size provided at least 95% power overall to demonstrate bioequivalence of the Test treatment to the Reference treatment for both AUC_{last} and C_{max} based on the assumption that the true ratio between Test treatment and Reference treatment for both AUC_{last} and C_{max} is 1.05. The power calculations assumed the estimates of within-subject standard deviations (SD) as 0.1405 for $\ln(AUC_{24})$ and 0.1147 for $\ln(C_{max})$. Assuming an approximate dropout rate of 10%, 20 subjects were recruited into the study to ensure 18 completers.

Results

Study population

All 20 enrolled subjects completed the study and were included in the PK and safety analyses. Subjects were all Chinese males, had an overall mean \pm SD age of 25.4 ± 2.1 years (range 22-29 years), weighed a mean \pm SD of 65.3 ± 6.8 kg (range 55.0-77.0 kg), and had an overall mean \pm SD BMI of 22.1 ± 1.2 kg/m² (range 20.1-24.0 kg/m²). None of the study subjects received prior or concomitant drug or non-drug treatments.

Pharmacokinetics

The mean (\pm SD) plasma linezolid concentration-time profiles for both treatments are displayed in Figure 1 and PK parameters summarized in Table 1. The absorption of the linezolid oral suspension formulation was slightly faster than that of the tablet formulation with the median T_{max} at 0.63 h and 1.50 h, respectively. Following attainment of C_{max} , mean linezolid plasma concentrations declined in parallel

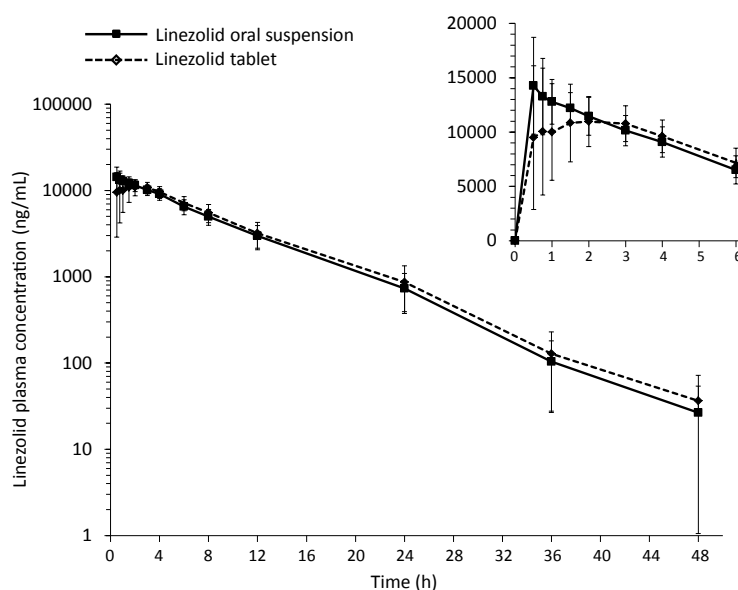


Figure 1: Mean (\pm SD) plasma linezolid concentration-time profiles following single oral doses of 600 mg oral suspension and 600 mg tablet formulations in healthy Chinese subjects (N=20); 0-48 h on log-linear scale, and 0-6 h on linear-linear scale [insert].

Parameter (Units)	Linezolid 600 mg tablet (Reference treatment) N=20	Linezolid 600 mg oral suspension (Test treatment) N=20
AUC _{inf} (µg·h/mL), mean (± SD)*	112.6 (24.9)	109.2 (21.7)
AUC _{last} (µg·h/mL), mean (± SD)*	112.0 (24.7)	108.9 (21.7)
C _{max} (µg/mL), mean (± SD)*	13.7 (3.5)	15.5 (3.5)
T _{max} (h), median (range)	1.50 (0.5–4.0)	0.63 (0.5–2.0)
t _{1/2} (h), mean (± SD)*	5.13 (0.92)	5.08 (0.70)

AUC_{inf}, area under plasma concentration–time curve from time zero extrapolated to infinite time; AUC_{last}, area under plasma concentration–time curve from time zero to the time of the last quantifiable concentration; C_{max}, maximum plasma concentration; SD: Standard Deviation; t_{1/2}, elimination half-life; T_{max}, time for maximum plasma concentration.

*Arithmetic mean.

Table 1: Descriptive summary of pharmacokinetic parameters of plasma linezolid following single oral doses of 600 mg oral suspension and 600 mg tablet formulations in healthy Chinese subjects.

Parameter (Units)	Geometric mean			90% CI for ratio (%)
	Reference (linezolid tablet), N=20	Test (linezolid oral suspension), N=20	Ratio* (%)	
AUC _{inf} (µg·h/mL)	109.8	107.2	97.65	92.92-102.63
AUC _{last} (µg·h/mL)	109.3	106.9	97.81	93.11-102.75
C _{max} (µg/mL)	13.3	15.2	113.67	105.26-122.75

AUC_{inf}, area under plasma concentration–time curve from time zero extrapolated to infinite time; AUC_{last}, area under plasma concentration–time curve from time zero to the time of the last quantifiable concentration; CI: Confidence Interval; C_{max}, maximum plasma concentration; CV, Coefficient of Variation.

*Ratio of adjusted geometric mean for Test treatment (linezolid 600 mg oral suspension) versus Reference treatment (linezolid 600 mg tablet).

Table 2: Statistical summary of treatment comparison.

between both formulations. Mean terminal t_{1/2} was about 5.1 h for both treatments. Total and peak exposures (AUC and C_{max}) to linezolid were similar between treatments following single-dose administration of the 600 mg oral suspension and the 600 mg tablet formulations. Inter-subject variability in exposure was also similar for both formulations, based on %CV values of 20-22% for AUC_{last} and AUC_{inf} and 23-26% for C_{max}.

Results of the statistical analysis for bioequivalence are presented in Table 2. The bounds of the 90% CI for the ratios of adjusted geometric means (linezolid oral suspension/tablet) for both AUC_{last} and C_{max} were completely within the 80 to 125% range, indicating that linezolid 600 mg oral suspension and 600 mg tablet formulations were bioequivalent. Results for AUC_{inf} were nearly identical to those for AUC_{last}, and were also completely within the 80 to 125% range.

Adverse events

There were no AEs reported following the treatment with the linezolid 600 mg oral suspension, and one subject receiving the linezolid 600 mg tablet reported one treatment-emergent AE of mild abdominal pain that was not treatment-related and that resolved after 3.4 h. There were no deaths, serious AEs, permanent discontinuations due to AEs, or dose reductions or temporary discontinuations due to AEs reported in this study, nor were there any clinically significant abnormalities in laboratory test data, vital signs, or ECG values.

Discussion

The primary objective of this study was to establish bioequivalence of a single dose of linezolid 600 mg oral suspension to 600 mg tablet

formulation in healthy Chinese male subjects to obtain regulatory approval for the oral suspension formulation. When administered as an oral suspension (600 mg), the total exposure (AUC) to linezolid was nearly identical to that following administration as an oral tablet (600 mg). The bounds of the 90% CIs for the ratios of adjusted geometric means for all three primary exposure comparisons AUC_{last}, AUC_{inf}, and C_{max}, were completely within the established equivalence limits of 80 to 125%. Based on these results, the linezolid 600 mg oral suspension is bioequivalent to the 600 mg tablet formulation and they are anticipated to be therapeutically equivalent and could be switched in subjects without any need for dose modification. The single doses of linezolid 600 mg oral suspension and 600 mg tablet formulation were safe and well-tolerated in healthy Chinese male subjects.

Linezolid has been available in China since 2007, but there are only a few reports on the PK and/or PD of linezolid in the Chinese population. The PK/PD profile of intravenous linezolid in eight critically ill Chinese patients with Gram-positive bacterial infections was reported to vary widely following twice-daily dose at 600 mg/dose, including a 5–7-fold difference in C_{max} (ranged from 5.57 to 27.08 mg/L with a mean ± SD of 15.70 ± 6.58 mg/L) and AUC₍₀₋₁₂₎ (ranged from 31.66 to 216.82 mg·h/L with a mean ± SD of 96.73 ± 56.45 mg·h/L) [24]. Wide linezolid serum exposures were also reported in Western populations following intermittent infusion (600 mg/12h) or continuous infusion (300 mg intravenous loading dose +900 mg continuous infusion, followed by 1200 mg/daily) [16]. Recently, Cai et al. evaluated the PK/PD properties of linezolid in healthy male Chinese volunteers with low (>50-≤ 55 kg) and high (≥ 80 kg) body weights following a single intravenous dose (600 mg/30 min) versus a weight-adjusted dose (10 mg/kg/30 min) [25]. Plasma concentrations were much higher in Chinese subjects with low body weight than in those with high body weight when a fixed dose was administered. Diminished serum concentrations following oral administration of linezolid have also previously been observed in obese Western populations [14], which is consistent with the reported population PK of linezolid indicating that body weight is one of the influential covariates on its clearance and distribution volume [15,26].

In our study in healthy Chinese adults, the observed geometric means for C_{max} were 15 µg/mL and 13 µg/mL and for AUC_{inf} were 107 µg·h/mL and 110 µg·h/mL, following single-dose linezolid 600 mg oral suspension and single-dose linezolid 600 mg oral tablet, respectively. These findings are in line with those reported in Western populations following a single-dose of 600 mg linezolid oral tablets and oral suspension [21]. The reported mean (± SD) for C_{max} were 11.00 (± 2.76) µg/mL and 12.70 (± 3.96) µg/mL and for AUC_{inf} were 80.80 (± 35.10) µg·h/mL and 91.40 (± 39.30) µg·h/mL, for oral suspension and oral tablet formulations, respectively. Similar results were reported from a randomized, open-label, two-way cross-over, single-dose PK study in 28 healthy adult Egyptian males [27], which also showed that the rate and extent of absorption of linezolid 600 mg oral suspension formulation was comparable to that of linezolid 600 mg tablet formulation; mean arithmetic AUC_{inf} for the suspension compared with the tablet were 120 µg·h/mL and 128 µg·h/mL, respectively, and mean arithmetic C_{max} were 9.4 µg/mL and 9.2 µg/mL, respectively [27].

Conclusions

Based on the results of our study, linezolid 600 mg oral suspension and linezolid 600 mg tablets are anticipated to be therapeutically equivalent in healthy Chinese subjects and could be switched in subjects without any need for dose modification. Both formulations were safe and well tolerated in this study.

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Conflict of Interest

This study was sponsored by Pfizer Inc. (www.clinicaltrials.gov identifier: NCT01055769). Jing Zhang and Yingyuan Zhang were the Principal Investigators for the study from Hua Shan Hospital, China. Ronnie Wang, Christine Alvey, Qiang Wang, Bharat Damle, and Huifen Faye Wang were employees of Pfizer Inc. The study sponsor, Pfizer Inc., and the manuscript authors were involved in study design; collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

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