Transl Clin Pharmacol. 2024 Dec;32(4):216-224
https://doi.org/10.12793/tcp.2024.32.e18
pISSN 2289-0882·eISSN 2383-5427

Translational and Clinical Pharmacology TCP

Original Article

Check for updates

Comparative pharmacokinetics study of two tablet formulations of delpazolid, a novel oxazolidinone class antibiotic

JaeEun Koh [1], **Juyoung Khwarg** [1], **Young Lag Cho** [2], **Kyung-Sang Yu** [1], and **Jae-Yong Chung** [3,*]

[1]Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul 03080, Korea
[2]LigaChem Biosciences, Inc., Daejeon 34002, Korea
[3]Department of Clinical Pharmacology and Therapeutics, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam 13620, Korea

OPEN ACCESS

Received: Aug 27, 2024
Revised: Sep 16, 2024
Accepted: Nov 20, 2024
Published online: Dec 18, 2024

***Correspondence to**
Jae-Yong Chung
Department of Clinical Pharmacology and Therapeutics, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
Email: mekka@snu.ac.kr

ORCID iDs
JaeEun Koh
https://orcid.org/0009-0009-0725-3450
Juyoung Khwarg
https://orcid.org/0000-0001-7097-2006
Young Lag Cho
https://orcid.org/0000-0002-5787-9605
Kyung-Sang Yu
https://orcid.org/0000-0003-0921-7225
Jae-Yong Chung
https://orcid.org/0000-0003-4188-2786

Trial Registration
ClinicalTrials.gov Identifier: NCT04939779

Funding
This study was sponsored by LigaChem Biosciences, Inc., Seoul, Republic of Korea.

Conflict of Interest
Young Lag Cho, PhD is an employee of LigaChem Biosciences, Inc. The other authors

ABSTRACT

Delpazolid is an oxazolidinone-class antibiotic under development for treating diseases caused by antimicrobial-resistant gram-positive bacteria. This study compared the pharmacokinetics (PK) and safety of two formulations of delpazolid 400 mg with distinct excipient compositions: Batch No. 3183817R (test drug) and Batch No. 1650006 (reference drug). A randomized, open-label, single-dose, two-way crossover study was conducted. The participants received a single oral dose of delpazolid 400 mg (test or reference) in each period, with serial blood samples collected up to 12 hours post-dose. The PK parameters of delpazolid were calculated using a noncompartmental method. The geometric mean ratios (GMRs) and its 90% confidence intervals (CIs) of the test drug to the reference drug were estimated for the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time zero to the last observation (AUC_{last}). Safety assessments were also conducted. Twenty-four participants completed the study as planned. The PK profiles of delpazolid were similar between the test and reference drugs. The GMRs (90% CIs) of the test to the reference for C_{max} and AUC_{last} were 1.1265 (0.8666–1.4644) and 1.0290 (0.9402–1.1261), respectively. The result of AUC_{last} met the bioequivalence criteria (0.8–1.25), but the 90% CI for C_{max} exceeded the upper limit of 1.25. Both drugs were safe and well tolerated. The two different delpazolid formulations showed comparable PK and safety profiles, indicating that the test drug is an appropriate alternative to the reference drug.

Trial Registration: ClinicalTrials.gov Identifier: NCT04939779

Keywords: Pharmacokinetics; Delpazolid; Bioequivalence; Tablets

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is caused by a strain of the *Mycobacterium tuberculosis* complex that is resistant to isoniazid and rifampicin, the two most potent first-line treatments for TB [1]. Global estimates indicate that, on average, 3.6% of newly diagnosed

do not have any conflict of interest for this study.

Reviewer

This article was reviewed by peer experts who are not TCP editors.

Author Contributions

Writing - original draft: Koh J; Writing - review & editing: Khwarg J, Cho YL, Yu KS, Chung JY.

patients with TB and 18% of previously treated patients with TB have MDR-TB or rifampicin-resistant TB (RR-TB) [2]. Although the annual number of patients who developed MDR-TB or RR-TB remained relatively stable from 2015 to 2020, there was a noticeable increase in 2021 [2]. This increase in drug-resistant TB remains a major public health concern [2]. Therefore, it is essential to develop new antibiotics to delay the emergence of drug resistance.

The current treatment recommendation for MDR-TB is a six-month BPaLM regimen consisting of bedaquiline, pretomanid, linezolid, and moxifloxacin [1]. Among these treatments, linezolid was the first oxazolidinone-class antibiotic approved by the U.S. Food and Drug Administration in 2000, targeting infections caused by multidrug-resistant gram-positive bacteria [2]. Oxazolidinones inhibit bacterial protein biosynthesis by interfering with the V domain of the bacterial 23S rRNA located at the A-site of the 50S ribosomal subunit [3]. However, the primary issues related to the clinical use of linezolid are its significant adverse effects, such as reversible myelosuppression, irreversible optic neuropathy, and peripheral neuropathy [4]. Therefore, substantial efforts have been made in the field of MDR-TB infections to discover next-generation oxazolidinones with enhanced antibacterial efficacy and improved safety profiles.

Delpazolid is an investigational oxazolidinone class antibiotic. It is being developed to treat diseases caused by antimicrobial-resistant gram-positive bacteria, namely vancomycin-resistant *enterococci*, methicillin-resistant *staphylococcus aureus* (MRSA), and *M. tuberculosis*. Delpazolid is expected to present improved safety over linezolid, particularly by reducing severe side effects. Notably, in a previous phase 1 study of delpazolid, no myelosuppression was observed at doses up to 1,200 mg BID during 21 days of repeated dosing [5]. Furthermore, some findings suggest that delpazolid has a greater advantage in diseases requiring long-term therapy, particularly in the context of managing TB, as the increased use of linezolid over time has led to the emergence of resistant strains [6]. Studies have shown that MDR-TB exhibits a 6.7% resistance rate to linezolid, whereas only a 0.8% resistance rate is observed for delpazolid [7]. Consequently, delpazolid could be a promising treatment to address the critical safety issues and the development of resistance associated with linezolid.

Previous clinical studies have revealed the pharmacokinetics (PK) characteristics of delpazolid. The PK characteristics of delpazolid in the dosage range of 50 to 3,200 mg were evaluated in a prior phase 1 single ascending dose study conducted in healthy adults [8]. In this study, delpazolid was rapidly absorbed after oral administration, reaching its maximum plasma concentration (C_{max}) within 1 hour [8]. Across the dosage range of 50 to 3,200 mg, C_{max} exhibited a linear increase, but the area under the plasma concentration-time curve (AUC) increased more than proportionally [8]. The mean plasma elimination half-life ($t_{1/2}$) of delpazolid was approximately 1.41–3.41 hours in the dosage range of 50 to 3,200 mg [8].

The effect of food on the PK and safety of delpazolid has also been investigated [9]. A slight delay in the time to reach C_{max} (T_{max}) was observed in the fed state compared with that in the fasted state [9]. However, as the overall systemic exposure to delpazolid remained consistent in both fed and fasted conditions, it was suggested that delpazolid could be administered regardless of food intake [9].

In response to concerns regarding genotoxicity and other uncertainties associated with titanium dioxide, it remains provisionally on the list of authorized additives, pending the development of adequate alternatives [10]. Accordingly, the excipient of the delpazolid tablet

was changed to a titanium-free formulation. The formulation was changed from Batch No. 1650006 (reference drug) to a new formulation, Batch No. 3183817R (test drug). Therefore, this study aimed to compare the PK and safety of two tablet formulations of delpazolid 400 mg, with different excipient compositions in healthy adults.

METHODS

This study was conducted at Seoul National University Bundang Hospital, Republic of Korea, in accordance with the Declaration of Helsinki and the guidelines of Korean Good Clinical Practices. This trial was registered in the Clinical Trial Registry (ClinicalTrials.gov: NCT04939779). The study protocol was approved by an independent ethics committee, the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB number: B-2010-643-001), and the Ministry of Food and Drug Safety of Korea. Written informed consent was obtained from all participants before their participation in the study.

Study population

Eligible individuals were healthy men or women aged 19 to 45 years, with no childbearing potential, a body mass index (BMI) between 18.0 and 28.0 kg/m^2, and a weight over 50 kg. Patients with a clinically significant history of disease, hypersensitivity to delpazolid, or drugs within the same class of antibiotics, such as linezolid, were excluded.

Study design

This randomized, open-label, single-dose, two-way crossover study included 24 healthy adult volunteers. The test drug was delpazolid 400 mg, a new formulation manufactured from Batch No. 3183817R, and the reference drug was delpazolid 400 mg, a previous formulation manufactured from Batch No. 1650006.

This study enrolled 24 individuals based on the coefficient of variation (CV) calculated from a previous food effect study on delpazolid [9]. Assuming an intrasubject CV of 27.5%, representing 60% of the total CV of 45.9%, a sample size of 24 provided approximately 74% power to show bioequivalence between the test and reference drugs.

Individuals were randomly assigned to one of the two sequences, A or B, at a ratio of 1:1. Individuals assigned to sequence A received the reference drug in period 1 and the test drug in period 2, while individuals assigned to sequence B received the test drug in period 1 and the reference drug in period 2. The wash-out period was two days between the two periods. The study drugs were orally administered in 150 mL of water after at least 10 hours of overnight fasting. Serial blood samples were collected at 0 (pre-dose) and 0.25, 0.5, 0.66, 0.83, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours post-dose for each period. Blood samples were collected in a heparinized tube for each sampling point, centrifuged at 4˚C and 2,095 g for 10 minutes, and stored at –70˚C until analysis.

Laboratory assay

Plasma concentrations of delpazolid were determined by protein precipitation, followed by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Delpazolid was extracted from plasma samples by protein precipitation with acetonitrile containing LCB01-0720 as the internal standard, followed by determination using validated

LC-MS/MS. Specifically, 100 μL of plasma samples were spiked with 10 μL of internal standard and 500 μL of acetonitrile, followed by centrifugation for 5 minutes at 13,000 rpm. Aliquots of 100 μL of the supernatant were collected, and 500 μL of acetonitrile were added to the resulting residue, followed by 10 minutes of vortexing. Subsequently, 1 μL of the reconstituted solution was injected into LC-MS/MS for analysis.

The LC-MS/MS analysis was performed using an Exion liquid chromatography system (SCIEX, Framingham, MA, USA) coupled to an API 4000(2) mass spectrometer (SCIEX). LC separation was achieved using a C_{18} column (3 μm, 2.0 mm × 75 mm) and gradient elution with 1 mM ammonium formate and acetonitrile solution as the mobile phase. MS/MS was performed with multiple reaction monitoring (MRM) in the positive electrospray ionization mode. The MS/MS transition (m/z) of 309.2 → 239.0 and 312.0 → 239.0 for delpazolid and the LCB01-0720 (internal standard), respectively, were selected for MRM.

A calibration curve for delpazolid in plasma was constructed by plotting the (delpazolid/internal standard) peak area ratios of the samples against concentrations ranging from 10 ng/mL (lower limit of quantification; LLOQ) to 20,000 ng/mL (upper limit of quantification). The linear regression equation was found to be "peak area ratio = 0.00114 × concentration + 0.000461" with a correlation coefficient (r) value for linearity in plasma samples of 0.9996. The back-calculated concentration in the calibrators was determined with an accuracy of 94.5 to 103.9% and precision (%CV) of 0.5 to 2.7%. Intra-batch quality control samples in the concentration range of 30 to 16,000 ng/mL were determined with an accuracy of 93.8 to 100.7% and precision (% CV) of 3.4 to 6.5%.

PK analysis

The PK parameters of delpazolid were calculated by a noncompartmental method using Phoenix WinNonlin® Version 8.3 (Pharsight, CA, USA). The primary PK parameters were the AUC from time zero to the last observation (AUC_{last}) and the C_{max}. The secondary PK parameters of interest included the area under the curve from time 0 extrapolated to infinity (AUC_{inf}), T_{max}, $t_{1/2}$, apparent total body clearance of the drug from the plasma (CL/F), and apparent volume of distribution of the drug after administration (V_d/F). The actual sampling time was used to calculate the PK parameters of delpazolid. Concentrations below the LLOQ (10 ng/mL) were excluded from PK analysis. Concentrations of delpazolid below the LLOQ prior to reaching C_{max} were considered zero, whereas those occurring after C_{max} were treated as missing values. The C_{max} and T_{max} were obtained directly from the observed plasma delpazolid concentrations. AUC_{last} was calculated from the plasma delpazolid concentration-time curve using the linear trapezoidal rule for increasing plasma levels and the logarithmic trapezoidal rule for decreasing plasma levels. Other derived PK parameters were calculated based on the elimination rate constant (λ_z), determined from the slope of the terminal phase of the plasma concentration-time curve, using the following formulations: $t_{1/2}$ determined by $\ln(2)/\lambda_z$, AUC_{inf} by adding AUC_{last} to the last observed concentration/λ_z, CL/F by Dose/AUC_{inf}, V_d/F by Dose/λ_z × AUC_{inf}.

Safety and tolerability assessment

Safety and tolerability were assessed by monitoring adverse events and evaluating vital signs (sitting blood pressure, pulse rate, and body temperature), physical examinations, 12-lead electrocardiography (ECG), and clinical laboratory evaluations (hematology, blood chemistry, and urinalysis).

https://doi.org/10.12793/tcp.2024.32.e18

Statistical analysis

The statistical analysis was performed using SAS® software version 9.4 (SAS Institute, Cary, NC, USA). PK analysis was performed on data from individuals with measurable plasma delpazolid concentrations in accordance with the planned PK sampling schedule, without any significant protocol deviations. Safety and tolerability were assessed in participants who received either the test or reference drug at least once. Outcomes, such as demographics, medical history, concomitant medications, safety assessments, plasma concentration, and PK parameters of delpazolid were summarized and compared between the test and reference drugs. The differences in least square means of log-transformed values of primary endpoint variables (C_{max} and AUC_{last}) were estimated from an analysis of variance (ANOVA) model, including sequence, period, and treatment as fixed effects, and subject nested within the sequence as random effects. The geometric mean ratios (GMRs) and its 90% confidence intervals (CIs) of the test to reference for C_{max} and AUC_{last} were estimated from back-transformation of the ANOVA results.

RESULTS

Demographics

A total of 25 individuals were randomized, and 24 completed the study as planned.
One individual withdrew consent before the administration of the study drug. The baseline demographic characteristics of the participants were similar across the two sequences, except for weight and BMI. The mean ± standard deviation values of age, height, weight, and BMI for the 24 randomized individuals were 25.96 ± 5.76 years, 175.01 ± 4.61 cm, 72.41 ± 7.3 kg, and 23.61 ± 1.91 kg/m^2, respectively. The variations in weight and BMI among individuals assigned to each sequence group were statistically significant (p = 0.0008 for weight and p = 0.0017 for BMI) when compared using an independent t-test.

PK profiles of delpazolid

PK analysis was performed on 24 individuals. The concentration-time profiles and estimated PK parameters of delpazolid were similar for the test and reference drugs (**Fig. 1**, **Table 1**).

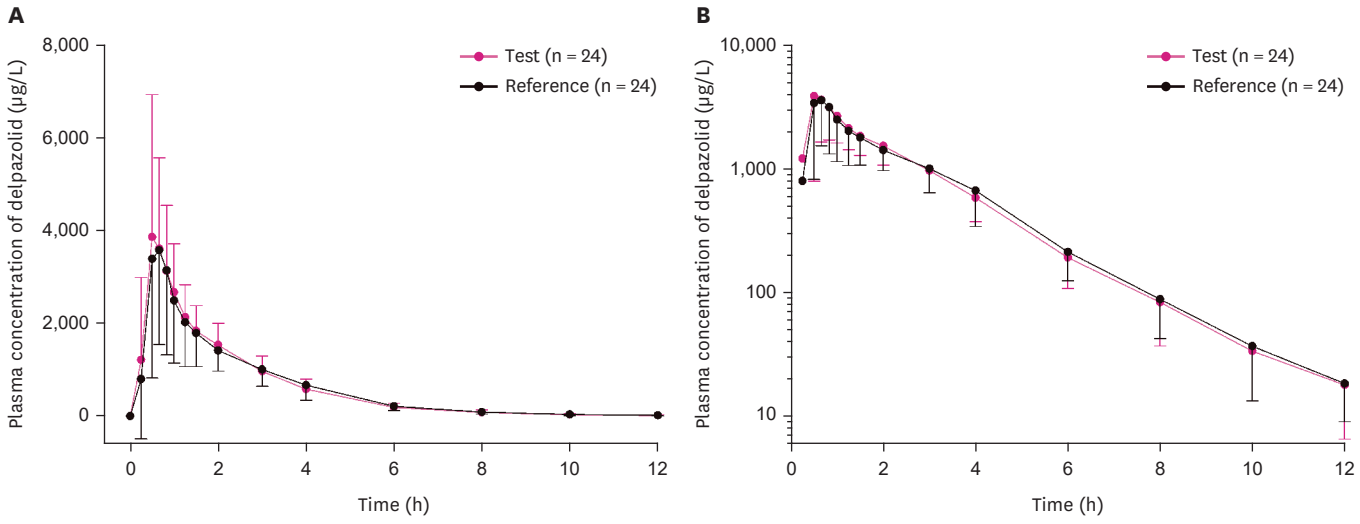

Figure 1. Mean plasma concentration-time profiles of delpazolid after a single oral administration of delpazolid 400 mg (A) in a linear scale and (B) in a semi-log scale. Error bars represent standard deviations.

https://doi.org/10.12793/tcp.2024.32.e18

Table 1. Summary of pharmacokinetic parameters of delpazolid after a single oral administration of delpazolid 400 mg

Pharmacokinetic parameters	Test (n = 24)		Reference (n = 24)	
	Mean ± SD	CV (%)	Mean ± SD	CV (%)
AUC_{last} (μg·h/L)	7,474.84 ± 2,270.59	30.4	7,319.39 ± 2,298.85	31.4
C_{max} (μg/L)	5,012.98 ± 2,451.42	48.9	4,525.10 ± 2,275.03	50.3
AUC_{inf} (μg·h/L)	7,517.05 ± 2,289.75	30.5	7,361.56 ± 2,311.14	31.4
T_{max} (h)	0.67 (0.25–3.00)		0.67 (0.50–4.00)	
$t_{1/2}$ (h)	1.56 ± 0.16	10.4	1.54 ± 0.17	11.2
CL/F (L/h)	57.11 ± 14.67	25.7	59.33 ± 17.57	29.6
V_d/F (L)	126.74 ± 30.45	24.0	130.35 ± 36.16	27.7

Data are presented as mean ± SD except for T_{max}, for which median (minimum–maximum) is presented.
SD, standard deviation; CV, coefficient of variation; AUC_{last}, area under the plasma concentration-time curve from time zero to the last observation; C_{max}, maximum plasma concentration; AUC_{inf}, area under the curve from time zero to infinity; T_{max}, time to reach maximum plasma concentration; $t_{1/2}$, terminal elimination half-life; CL/F, apparent total clearance of the drug from plasma after administration; V_d/F, apparent volume of distribution of the drug after administration.

Individual changes in the C_{max} and AUC_{last} values of delpazolid between study drugs are shown in **Fig. 2**. The GMRs (90% CIs) of the test drug to the reference drug for the C_{max} and AUC_{last} of delpazolid were 1.1265 (0.8666–1.4644) and 1.0290 (0.9402–1.1261), respectively (**Table 2**). The results of AUC_{last} fell within the conventional bioequivalence criteria (0.8–1.25), but the upper confidence limits of C_{max} lay outside, above 1.25.

Table 2. GMR and 90% CI of delpazolid after a single oral administration of delpazolid 400 mg

Pharmacokinetic parameters	Geometric mean		GMR* (90% CI)
	Test (n = 24)	Reference (n = 24)	
C_{max} (μg/L)	4,419.68	3,923.35	1.1265 (0.8666–1.4644)
AUC_{last} (μg·h/L)	7,200.87	6,998.25	1.0290 (0.9402–1.1261)

GMR, geometric mean ratio; CI, confidence interval; C_{max}, maximum plasma concentration; AUC_{last}, area under the plasma concentration-time curve from time zero to the last observation.
*GMR of test to reference.

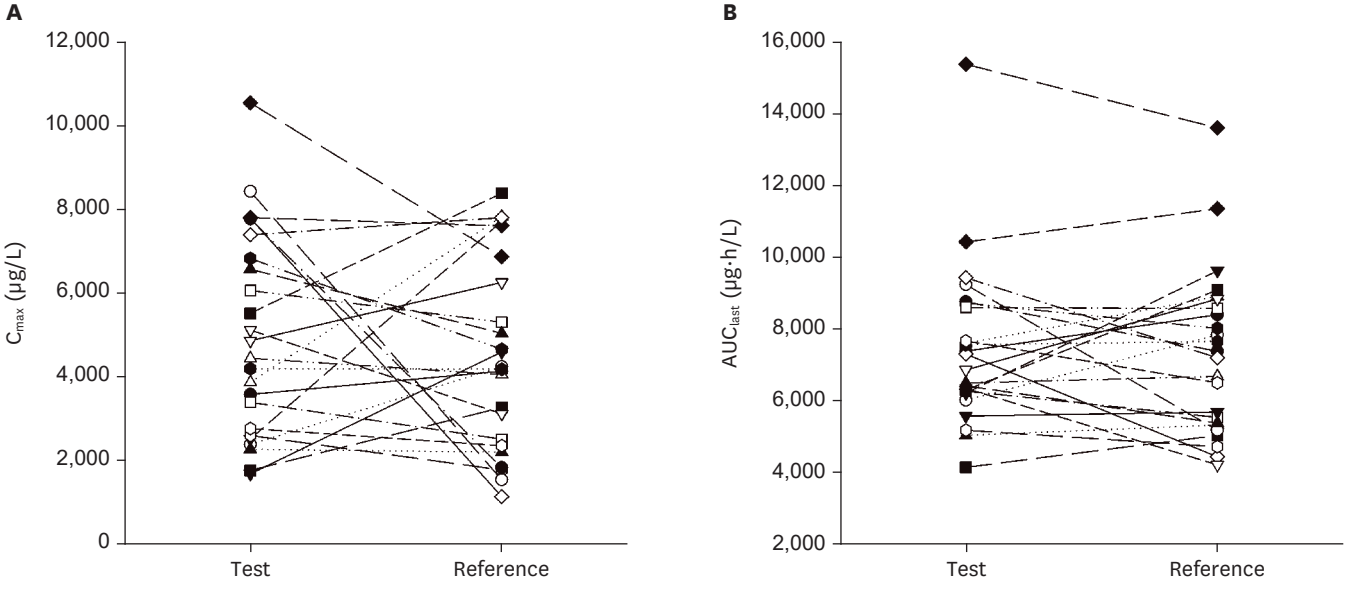

Figure 2. Comparison of individual (A) C_{max} and (B) AUC_{last} of delpazolid after a single oral administration of delpazolid 400 mg.
C_{max}, maximum plasma concentration; AUC_{last}, area under the plasma concentration-time curve from time zero to the last observation.

https://doi.org/10.12793/tcp.2024.32.e18

Table 3. Summary of treatment-emergent adverse events of delpazolid 400 mg

Systemic organ class preferred term	Test (n = 24)		Reference (n = 24)		All participants (n = 24)	
	No. (%)	No. of event	No. (%)	No. of event	No. (%)	No. of event
Individuals with at least one TEAEs	4 (16.7)	4	6 (25.0)	6	8 (33.3)	10
Eye disorders			1 (4.2)	1	1 (4.2)	1
Abnormal sensation in eye			1 (4.2)	1	1 (4.2)	1
General disorders and administration site conditions	1 (4.2)	1			1 (4.2)	1
Pyrexia	1 (4.2)	1			1 (4.2)	1
Investigations			1 (4.2)	1	1 (4.2)	1
Blood creatine phosphokinase increased			1 (4.2)	1	1 (4.2)	1
Musculoskeletal and connective tissue disorders	1 (4.2)	1			1 (4.2)	1
Pain in extremity	1 (4.2)	1			1 (4.2)	1
Nervous system disorders	2 (8.3)	2	3 (12.5)	3	5 (20.8)	5
Dizziness			1 (4.2)	1	1 (4.2)	1
Headache	2 (8.3)	2	2 (8.3)	2	4 (16.7)	4
Vascular hemorrhage disorders			1 (4.2)	1	1 (4.2)	1
Epistaxis			1 (4.2)	1	1 (4.2)	1

TEAE, treatment-emergent adverse events.

Safety and tolerability

Safety and tolerability assessments were performed in 24 individuals who received at least one dose of the study drug. A total of 10 treatment-emergent adverse events (TEAEs) occurred in eight individuals (33.3%) (**Table 3**). Specifically, four TEAEs in four individuals (16.7%) occurred after administration of the test drug, and six TEAEs in six individuals (25.0%) occurred after administration of the reference drug. Among the 10 TEAEs, a total of five TEAEs in five individuals (20.8%) were regarded as adverse drug reactions (ADRs). Three ADRs in three individuals (12.5%), including pyrexia (n = 1) and headache (n = 2), occurred after administration of the test drug. Two ADRs in two individuals (8.3%), including dizziness (n = 1) and headache (n = 1), occurred after administration of the reference drug. Abnormal sensations in the eyes (n = 1), increased blood creatine phosphokinase (n = 1), pain in the extremities (n = 1), headache (n = 1), and epistaxis (n = 1) were determined to be unrelated to the study drug. All TEAEs were mild in severity and resolved without sequelae. No serious adverse events, deaths, or study withdrawals due to adverse events occurred.

In terms of clinical laboratory evaluations, there was one case with an increasing tendency in blood creatine phosphokinase levels that subsequently resolved spontaneously without sequelae. No other clinically significant changes were observed in the clinical laboratory evaluations, vital signs, physical examination, or 12-lead ECG. The test and reference drugs were both safe and well-tolerated, showing similar safety profiles.

DISCUSSION

In this study, we compared the PK and safety profiles of two tablet formulations of delpazolid. The point estimates and 90% CIs of the GMR for the AUC_{last} of delpazolid met the conventional bioequivalence criteria of 0.80 to 1.25. In terms of C_{max}, the point estimates of GMR were within the range of 0.8 to 1.25, but the 90% confidence limits of GMR lay slightly outside the bioequivalence criteria, with the upper limit being > 1.25. The concentration-time profiles of delpazolid were similar for the test and reference drugs. Both study drugs were safe and well-tolerated, exhibited no serious adverse events, and had similar safety profiles. Therefore, subsequent phase 2 trials, one in patients with pulmonary TB (NCT04550832)

https://doi.org/10.12793/tcp.2024.32.e18

and one in patients with MRSA bacteremia (NCT05225558), were conducted using the formulation of the test drug.

In the present study, high CVs (%) of C_{max} of delpazolid were observed, with values of 48.9% for the test drug and 50.3% for the reference drug. Considering the 2-period, 2-sequence crossover design, an additional calculation of the intrasubject variability for delpazolid was attempted; however, the residual of covariance parameter estimates for C_{max} did not yield meaningful results.

Therefore, an additional PK analysis was performed, excluding the data from individual R1009, based on the largest deviation in the test/reference ratio of C_{max} among all individuals (**Supplementary Fig. 1**). Following the exclusion of outlier R1009, the GMR (90% CI) for the C_{max} and AUC_{last} of delpazolid were 1.0372 (0.8168–1.3172) and 1.0061 (0.9236–1.0960), respectively. Furthermore, the intrasubject variability for the C_{max} of delpazolid was 49.78%, as calculated from the residual yield of the ANOVA model. This value was notably higher than the empirically assumed value (27.5%) from a previous food effect study on delpazolid [9], which was used for the sample size calculation in the present study design. Several possible reasons for these discrepancies include the influence of food intake on the intrasubject variability obtained from food effect studies, such as potential C_{max} delays [9]. Thus, the accuracy of the intrasubject variability of the reference drug under fasting conditions could be compromised. Additionally, the number of individuals in the previous food effect study was close to the minimum required (17), which may not have constituted an adequate sample size [9].

Considering the high intrasubject variability of delpazolid calculated in this study, a larger sample size may be necessary for further bioequivalence evaluation. A sample size calculation indicated that > 70 participants were required to achieve > 78% power for the bioequivalence test.

The mean C_{max} of the test drug was slightly higher than that of the reference drug; however, this difference was suggested to have less pharmacological significance considering the pharmacodynamic (PD) characteristics of delpazolid. The major PK/PD parameter correlating with the antibacterial effect of oxazolidinone-class antibiotics is the 24-hour AUC/minimum inhibitory concentration (MIC) ratio [11]. Thus, the bactericidal activity of oxazolidinone antibiotics shows very little dependence on the drug concentration [11]. As with other oxazolidines, delpazolid has shown that the AUC/MIC parameters best predicted its antibacterial activity among the PK/PD parameters, including AUC/MIC, C_{max}/MIC, and time above the MIC [12]. Since the GMR and its 90% CIs for the AUC_{last} of delpazolid fell within the bioequivalence criteria, it is suggested that there would be no difference in clinical efficacy between the test and reference drugs. This was consistent with the results showing similarities in the PK and safety profiles between the two study drugs.

A limitation of this study is that a larger sample size may be warranted, given the high intrasubject variability observed with delpazolid in this study. Alternatively, a reference-scaled average bioequivalence approach involving a three- or four-period replicated design may be more appropriate than a two-period, two-sequence crossover design.

Delpazolid, a novel oxazolidinone-class antibiotic with two different formulations and batches, showed similar PK characteristics, and both drugs were safe and well-tolerated. The similarity between the two study drugs indicates that the test drug is an appropriate alternative to the reference drug.

https://doi.org/10.12793/tcp.2024.32.e18

SUPPLEMENTARY MATERIAL

Supplementary Figure 1

Box plot of the test to reference ratio of C_{max} of delpazolid after a single oral administration of delpazolid 400 mg. C_{max} data points outside the 10th and 90th percentiles are presented as symbols.

REFERENCES

1. World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2022.
2. World Health Organization. Global tuberculosis report 2022. Geneva: World Health Organization; 2022.
3. Foti C, Piperno A, Scala A, Giuffrè O. Oxazolidinone antibiotics: chemical, biological and analytical aspects. Molecules 2021;26:4280. PUBMED | CROSSREF
4. Gerson SL, Kaplan SL, Bruss JB, Le V, Arellano FM, Hafkin B, et al. Hematologic effects of linezolid: summary of clinical experience. Antimicrob Agents Chemother 2002;46:2723-2726. PUBMED | CROSSREF
5. Choi Y, Lee SW, Kim A, Jang K, Nam H, Cho YL, et al. Safety, tolerability and pharmacokinetics of 21 day multiple oral administration of a new oxazolidinone antibiotic, LCB01-0371, in healthy male subjects. J Antimicrob Chemother 2018;73:183-190. PUBMED | CROSSREF
6. Tsiodras S, Gold HS, Sakoulas G, Eliopoulos GM, Wennersten C, Venkataraman L, et al. Linezolid resistance in a clinical isolate of *Staphylococcus aureus*. Lancet 2001;358:207-208. PUBMED | CROSSREF
7. Zong Z, Jing W, Shi J, Wen S, Zhang T, Huo F, et al. Comparison of *in vitro* activity and MIC distributions between the novel oxazolidinone delpazolid and linezolid against multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis* in China. Antimicrob Agents Chemother 2018;62:e00165-18. PUBMED | CROSSREF
8. Cho YS, Lim HS, Lee SH, Cho YL, Nam HS, Bae KS. Pharmacokinetics, pharmacodynamics, and tolerability of single-dose oral LCB01-0371, a novel oxazolidinone with broad-spectrum activity, in healthy volunteers. Antimicrob Agents Chemother 2018;62:e00451-18. PUBMED | CROSSREF
9. Sunwoo J, Kim YK, Choi Y, Yu KS, Nam H, Cho YL, et al. Effect of food on the pharmacokinetic characteristics of a single oral dose of LCB01-0371, a novel oxazolidinone antibiotic. Drug Des Devel Ther 2018;12:1707-1714. PUBMED | CROSSREF
10. Commission Regulation (EU) 2022/63 of 14 January 2022 amending annexes II and III to regulation (EC) No 1333/2008 of the European parliament and of the council as regards the food additive titanium dioxide (E 171) (text with EEA relevance). Official Journal of the European Union (Jan 18, 2022). Brussels: European Union; 2022.
11. Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am 2003;17:479-501. PUBMED | CROSSREF
12. Cho YS, Lim HS, Cho YL, Nam HS, Bae KS. Multiple-dose safety, tolerability, pharmacokinetics, and pharmacodynamics of oral LCB01-0371 in healthy male volunteers. Clin Ther 2018;40:2050-2064. PUBMED | CROSSREF