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Original Article

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Pharmacokinetics and bioequivalence study of candesartan cilexetil tablet in Chinese volunteers under fasting condition: an open-label, randomized-sequence, 2-period crossover study

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ABSTRACT

Candesartan is an antihypertensive agent that acts on an angiotensin II receptor. Candesartan cilexetil is a prodrug that is converted into the active form of candesartan during intestinal absorption. This study aimed to assess the pharmacokinetics and bioequivalence of a reference and a test formulation of candesartan cilexetil tablets in healthy Chinese volunteers. A randomized, open-label, single-dose, crossover study was conducted with two treatment periods. Forty-eight healthy Chinese volunteers participated under fasted conditions. Qualified subjects were randomly divided into two groups (1:1 ratio) to receive either the test or reference formulation first. A washout period of 14 days separated the administration of the two formulations. Blood samples were collected at specific time points and analyzed for candesartan concentration using Ultra High-Performance Liquid Chromatography Tandem Mass Spectrometry (UPLC-MS/MS). The maximum concentration (C_{max}), the AUC from time zero to the last measured time point (AUC_{0-t}) and the AUC from time zero to infinity ($AUC_{0-\infty}$) fell within the bioequivalence range of 80% to 125%. These results suggest that the test and reference formulations of candesartan cilexetil tablets are bioequivalent, meaning they have similar rates and extents of absorption in healthy Chinese volunteers. No serious adverse events or side effects were reported throughout the study.

Keywords: Candesartan Cilexetil; Bioequivalence; Pharmacokinetics

INTRODUCTION

Candesartan cilexetil is a prodrug, meaning it's converted to its active form, candesartan, during absorption in the gut. Candesartan acts by selectively blocking the AT1 subtype of angiotensin II receptors on vascular smooth muscle cells. This antagonism prevents

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angiotensin II from causing blood vessel constriction, ultimately lowering blood pressure [1]. Studies suggest that candesartan offers a more potent and sustained blood pressure reduction compared to other angiotensin II receptor antagonists [2]. Additionally, it has shown efficacy in treating left ventricular heart failure in adults [3,4].

Candesartan cilexetil tablets, launched under the brand name ATACAND® by AstraMerck in the US (June 1998), have been a mainstay in clinical practice for many years [5]. However, limited pharmacokinetic data exists specifically for the Chinese population, despite reports from abroad [6,7]. The introduction of candesartan cilexetil tablets by Zhejiang Nuode Pharmaceutical Co., Ltd. is expected to increase market competition, improve drug accessibility, potentially lower prices, and ultimately enhance patient compliance.

This study aims to evaluate the bioequivalence and tolerability of the candesartan cilexetil tablets under development by Zhejiang Nuode Pharmaceutical Co., Ltd., compared to a well-established reference product, in healthy Chinese volunteers under fasted conditions.

METHODS

Study population

Healthy Chinese volunteers aged over 18 years were enrolled in the study. Male participants had a minimum weight of 50 kg, while female participants weighed at least 45 kg, with a body mass index (BMI) ranging from 19 to 26. Prior to study entry, subjects underwent a comprehensive interview covering medical history, needle phobia, smoking and drinking habits, allergies, medication usage within the last 30 days, participation in blood donation or any drug clinical trial within the past 3 months, history of drug abuse, contraceptive status, and menstrual history for females.

Additionally, subjects underwent a series of routine physical examinations, including vital sign monitoring (blood pressure, pulse, and temperature), electrocardiograms, and laboratory tests (hematology, blood biochemistry, coagulation function, infectious disease screening, urinalysis, alcohol testing, and drug abuse screening). Participants with any clinically significant abnormalities detected during these assessments were excluded from the study.

Trial design

This single-center, open-label, randomized-sequence, single-dose, two-period crossover study was conducted at Wuhan Pulmonary Hospital in China. The study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Wuhan Pulmonary Hospital (approval No. 2021019) and the China National Medical Products Administration (approval No. CTR20213213). Clinical investigators thoroughly explained the study's purpose and risks to all eligible subjects, who then provided written informed consent before participation.

Eligible subjects were admitted to the research center two days before the trial began. Under fasting conditions, participants were randomly assigned in a 1:1 ratio using a computer-generated random number table to receive a single dose of 8 mg of either the experimental or reference formulation of candesartan cilexetil tablets in Period 1, followed by the alternative formulation in Period 2, with a 14-day washout period between doses. The test formulation (8 mg) was provided by Zhejiang Nuode Pharmaceutical Co., Ltd. (Zhejiang, China), and the

reference formulation (8 mg) was provided by KOKANDO CO., LTD. Kureha Plant (Toyama, Japan). Medication was swallowed with 240 mL of warm water. Subjects fasted for at least 10 hours before administration, avoided staying up late, and ensured sufficient sleep. They were also instructed not to drink water before and within 1 hour after drug administration. Standardized meals were provided 4 and 10 hours after administration.

Approximately 3 mL of venous blood was collected before administration (0 h) and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 24, 36, and 48 hours after administration. Blood samples were collected in pre-numbered, pre-cooled K_2EDTA anticoagulation tubes, gently mixed, and placed in an ice bath immediately, then transferred to the sample processing room as soon as possible. Samples were centrifuged within 60 minutes of collection, stored in a −20°C (< −10°C) refrigerator within 120 minutes, and transferred to a −70°C (< −60°C) refrigerator after complete freezing. After each sampling cycle, samples were transported in a cold chain at −70°C (≤ −60°C), without freezing and thawing. Candesartan cilexetil is rapidly hydrolyzed into candesartan in the body; thus, the concentration of candesartan in plasma was measured.

Throughout the trial, participants were prohibited from smoking, consuming alcohol, eating diets rich in xanthines and caffeine, engaging in vigorous exercise, or staying in bed for long periods. Subjects were under continuous medical observation throughout the study.

Determination of plasma concentrations

The plasma concentration of candesartan was determined by high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) after the completion of both periods [8,9].

The plasma concentration of Candesartan was determined by ultra-high performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). Blood concentrations of Candesartan were performed at Waters Acquity UPLC (Canton, MA, USA). The chromatography was performed on a Waters Acquity UPLCBEHC18 (50 mm × 2.1 mm) column with a particle size of 1.7 μm and a box temperature of 30ºC. The internal standard was Candesartan D4. The mobile phase was 0.2% ammonium acetate acetonitrile water, and the volume ratio was 20:80. The flow rate was 0.4 mL/min. The sample pretreatment method was protein precipitation (precipitant:0.2% acetonitrile). Ionization and detection of Candesartan and Candesartan D4 are performed on a triple quadrupole mass spectrometer, operating in multiple reaction monitoring and negative ionization modes. The ionic transition of protolation precursor → product was quantitatively monitored: Candesartan m/z 440.9→263.0 and Candesartan D4 m/z 444.6→265.1 (internal standard). The linear range of plasma candesartan assay was 0.400 ng/mL–240.000 ng/mL, and the lower limit of quantification was 0.400 ng/mL. No significant matrix effect was observed. After four freeze-thaw cycles of −20°C to room temperature and −80°C to 0°C, the analyte was stabilized in human plasma and its stability was confirmed after process.

Safety assessment

During the study, the safety of the test and reference preparations was assessed through various measures including monitoring vital signs (blood pressure, pulse, and temperature), conducting physical examinations, electrocardiograms, routine blood and urine analyses, and blood biochemical tests (such as liver and kidney function, and electrolytes). Vital signs were measured at admission, before administration (0 h), and at 2, 4, 6, 8, 12, 24, 36, and 48 hours after administration. Additionally, any adverse events were recorded throughout the study period.

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Pharmacokinetic and statistical analyses

To candesartan, the dose and corresponding blood concentration data for each subject were analyzed using Phoenix WinNonLin® 8.2 software (Pharsight Corporation, Sunnyvale, CA, USA) based on pharmacokinetic/pharmacodynamic principles (PK/PD). The following pharmacokinetic parameters were calculated using the software's Non-compartmental analysis module:

- T_{max}: Time to reach maximum concentration
- C_{max}: Maximum concentration
- AUC_{0-t}: Area under the curve from time zero to the last measured time point
- $AUC_{0-\infty}$: Area under the curve from time zero to infinity
- λz: Terminal elimination rate constant
- $t_{1/2}$: Half-life

Bioequivalence test

The primary pharmacokinetic parameters for bioequivalence assessment (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) for candesartan were log-transformed based on the Bioequivalence Standards (BES) guidelines. Statistical analysis was performed using SAS® 9.4 software (SAS Institute Inc., Cary, NC, USA) with a mixed-effects model (Proc Mixed) and multi-factor ANOVA. Equivalence testing was conducted using a two-sided, upper and lower confidence interval approach. The least squares geometric mean ratio (test formulation/reference formulation) and the corresponding 90% confidence interval were calculated for each major pharmacokinetic parameter (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$).

RESULTS

Subjects

A total of 48 healthy Chinese volunteers (mean age 27 ± 6 years, weight 66.1 ± 8.0 kg, height 169.7 ± 6.7 cm, BMI 23 ± 2 kg/m^2) participated in the study (**Table 1**). Two subjects (4.17%) voluntarily withdrew before completing all phases of the study.

Candesartan in pharmacokinetics

Table 2 summarizes the average pharmacokinetic parameters of candesartan following a single oral dose of 8mg tablets (test and reference formulations) administered on an empty stomach to 48 healthy Chinese volunteers. The mean C_{max} of candesartan was 62.231 ng/mL (standard deviation: 26.011 ng/mL) for the test formulation and 68.690 ng/mL (standard deviation: 22.029 ng/mL) for the reference formulation. The AUC_{0-t} for the test formulation was 871.3 h*ng /mL (standard deviation: 205.3 ng/mL) and $AUC_{0-\infty}$ was 911.9 h*ng /mL (standard deviation: 214.9 h*ng /mL). With the reference formulation, the corresponding values were 911.0 ng/mL (standard deviation: 211.9 h*ng /mL) and 955.5 h*ng /mL (standard deviation: 227.9 h*ng /mL). The corresponding T_{max} was 4.68 hours (standard deviation: 1.46 hours) for the test group and 4.41 hours (standard deviation: 1.35 hours) for the reference group.

Table 1. Demographic data of the volunteers (n = 48)

	Age (yr)	Weight (kg)	Height (cm)	BMI (kg/m^2)
Mean ± SD	27 ± 6	66.1 ± 8.0	169.7 ± 6.7	23 ± 2
Minimum	19	50	154	19
Maximum	41	84.4	182.5	26

SD, standard deviation; BMI, body mass index.

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Table 2. Mean [SD] pharmacokinetic parameters of candesartan after single-dose administration of 2 8-mg tablet formulations of candesartan cilexetil tablets in 48 fasting, healthy Chinese volunteers

Pharmacokinetic parameters (units)	Mean ± SD (CV%)	
	Test (n = 46)	Reference (n = 48)
C_{max} (ng/mL)	62.231 ± 26.011 (41.80)	68.690 ± 22.029 (32.07)
AUC_{0-t} (h*ng/mL)	871.3 ± 205.3 (23.56)	911.9 ± 214.9 (23.57)
$AUC_{0-\infty}$ (h*ng/mL)	911.0 ± 211.9 (23.26)	955.5 ± 227.9 (23.86)
*T_{max} (h)	4.68 ± 1.46 (31.20)	4.41 ± 1.35 (30.61)
$t_{1/2}$ (h)	10.70 ± 3.16 (29.55)	10.26 ± 3.29 (32.11)
λz	0.07 ± 0.02 (26.83)	0.07 ± 0.02 (26.31)

SD, standard deviation; AUC_{0-t}, area under the curve from time 0 to the last measurable concentration; $AUC_{0-\infty}$, area under the curve from time 0 to the infinite time; T_{max}, time to reach the peak concentration; t½, terminal half-life; λz, terminal disposition rate constant.
*T_{max} is expressed as the median (minimum, maximum).

The mean half-life ($t_{1/2}$) data for both formulations is included in **Table 2.** The mean plasma concentration-time profiles of candesartan for the test and reference formulations are presented in **Fig. 1.**

Table 3 summarizes the bioequivalence evaluation of the main pharmacokinetic parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) for candesartan. The 90% confidence intervals of the least squares geometric mean ratios for all parameters between the test and reference formulations fell within the predefined bioequivalence range of 80.00% to 125.00%. These results indicate that the test and reference formulations of candesartan cilexetil tablets are bioequivalent under fasting conditions in terms of their rate and extent of absorption.

Tolerability and safety

Test Formulation Group: Three out of 46 subjects (6.5%) taking the test formulation experienced a total of five adverse events, all of which were mild (severity level 1). These events included:

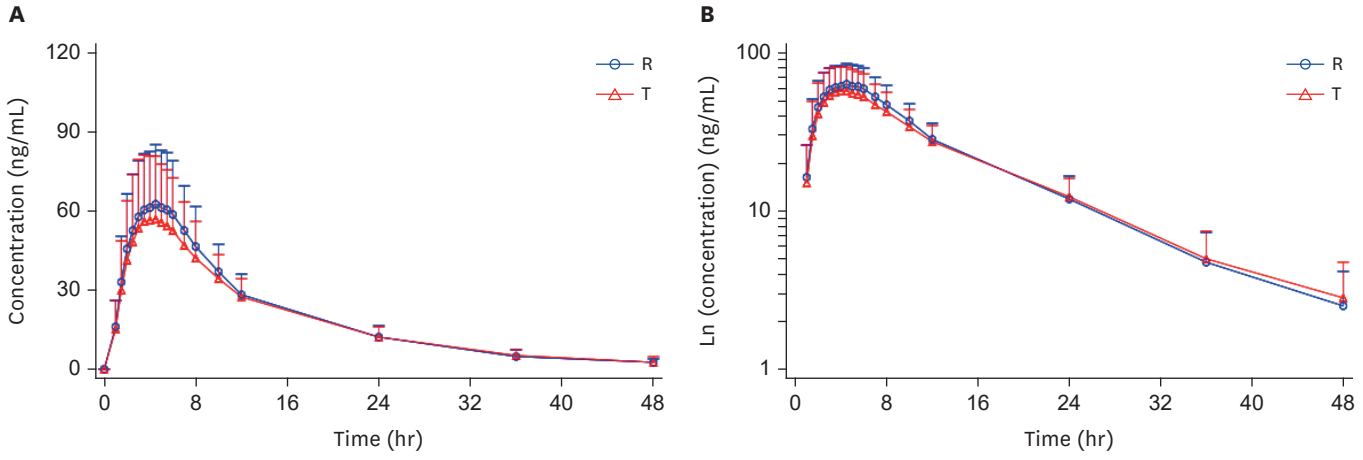

Figure 1. Mean [SD] plasma drug concentrations over 48 hours after single-dose administration of two 8-mg tablet formulations of candesartan cilexetil tablets in 48 fasting, healthy Chinese volunteers.

Table 3. Equivalence evaluation of main pharmacokinetic parameters (CI method) (BES)

Parameters (units)	Least squares geometric mean and ratio					Inter individual variation (%)	Individual variation (%)
	Test (n = 46)	Reference (n = 48)	T/R ratio (%)	Freedom	90% CI of T/R ratio (%)		
C_{max} (ng/mL)	57.991	65.221	88.91	44	82.98–95.28	29.84	19.98
AUC_{0-t} (h*ng/mL)	843.8	888.4	94.98	44	91.25–98.86	19.72	11.49
$AUC_{0-\infty}$ (h*ng/mL)	890.1	929.8	95.73	42	91.63–100.01	19.60	12.31

CI, confidence interval; BES, Bioequivalence Standards.

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- One case of elevated C-reactive protein
- Two cases of epistaxis (nosebleed)
- One case of anemia
- One case of elevated triglyceride

No serious adverse reactions were reported in the test group.

Reference Formulation Group: Two out of 48 subjects (4.2%) taking the reference formulation experienced mild (severity level 1) adverse events, Including elevated blood bilirubin and elevated triglyceride each. No serious adverse reactions were reported in the reference group.

Conclusions

This single-dose, fasting study investigated the bioequivalence and tolerability of a test formulation of 8mg candesartan cilexetil tablets compared to a reference formulation in healthy Chinese volunteers. Our findings demonstrate that the test formulation is bioequivalent to the reference formulation in terms of both the rate and extent of candesartan absorption. Additionally, both formulations were well-tolerated, with a low incidence of mild adverse events observed.

DISCUSSION

Hypertension, a prevalent chronic cardiovascular disease, is a major risk factor for serious complications such as heart failure, myocardial infarction (heart attack), stroke, and kidney failure [10,11]. Myocardial hypertrophy, thickening of the heart muscle, plays a critical role in hypertensive heart damage and significantly impacts mortality rates in hypertensive patients [12]. Fortunately, lowering blood pressure can effectively reduce the risk of these fatal cardiovascular events [13]. Candesartan cilexetil is an angiotensin II receptor blocker medication used to treat hypertension. It has also been shown to be effective in some adults with heart failure, especially when combined with angiotensin-converting enzyme inhibitors. These benefits are consistent with findings from controlled trials involving various classes of antihypertensive drugs [14]. Candesartan can be used alone or combined with other blood pressure medications, with minimal reported drug interactions, particularly with medications metabolized by the cytochrome P450 system [15]. Additionally, food intake does not significantly affect the therapeutic effect of candesartan cilexetil [16].

Following oral administration, candesartan cilexetil is rapidly converted to its active form, candesartan, in the body. Approximately 30% of candesartan is eliminated through urine, while the remaining 70% is excreted in feces [15,17]. This study specifically measured plasma concentrations of candesartan. The observed T_{max} (time to reach maximum concentration) in this study aligns with previously reported literature values of 3–5 hours for candesartan [1,2,6]. Considering candesartan's $t_{1/2}$ of around 9 hours, a 14-day washout period was deemed sufficient to ensure complete elimination of the drug from the body before the next dosing period. Since food has minimal impact on candesartan absorption [16], this study employed a fasting design.

The validated UPLC-MS/MS method used in this study adheres to relevant regulations and offers high sensitivity and specificity for quantifying candesartan blood concentrations [7].

A crossover design was chosen for the bioequivalence assessment as it effectively minimizes inter-subject variability. The study demonstrated bioequivalence between the test and reference formulations under fasted conditions. The 90% confidence interval of the least squares geometric mean ratio for the main pharmacokinetic parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) fell within the predetermined bioequivalence range of 80.00% to 125.00%. Notably, no serious adverse events or withdrawals due to adverse events were reported during the bioequivalence study. This indicates good tolerability for both formulations, consistent with findings from other clinical trials [6,18-21].

This study contributes valuable data to the growing body of evidence supporting the use of candesartan cilexetil for hypertension treatment. The demonstration of bioequivalence between the test and reference formulations provides clinicians with additional options for selecting appropriate antihypertensive medications.

However, one limitation of this study is the relatively young age of the participating volunteers (mean age 27 years). Given that hypertension is more prevalent in older populations, the pharmacokinetic profile of candesartan in elderly patients remains to be elucidated. Future studies specifically designed to evaluate the safety, efficacy, and pharmacokinetics of candesartan in elderly hypertensive patients are warranted to inform clinical application in this population.

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