Bioequivalence Study of Azilsartan in Healthy Chinese Subjects

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Research Article

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Abstract

Objective

To study the bioequivalence of generic Azilsartan tablet and original drug in Chinese healthy subjects under single dose fasting and postprandial conditions.

Methods

A single-center, randomized, open, single-dose, double-cycle, double-cross clinical trial was designed. For fasting and postprandial tests, 30 healthy subjects were included for random cross-administration, respectively. The concentration of Azilsartan in human plasma was determined by liquid chromatographer-tandem mass spectrometry (LC-MS/MS) after a single oral administration of test preparation and reference preparation 20mg (1 tablet). The pharmacokinetic parameters were calculated by WinNonlin8.2 software, and the equivalence was evaluated by SAS 9.4.

Results

The main pharmacokinetic parameters of test preparation and reference preparation of Azilsartan tablets in fasting test group were as follows: AUC_{0-t} was ($1.51\times10^4\pm3511.19$) and ($1.58\times10^4\pm3642.97$) h•ng•mL^{-1}, $AUC_{0-\infty}$ was ($1.54\times10^4\pm3692.29$) and ($1.62\times10^4\pm3784.64$) h•ng•mL^{-1}, C_{max} was (2055.00±438.70) and (2306.67±534.82) ng•mL^{-1}, T_{max} was (2.89±1.38) and (1.99±0.58) h, and $t_{1/2}$ was (9.68±1.02) and (9.76±0.90) h, respectively. The main pharmacokinetic parameters of the test preparation and reference preparation of Azilsartan tablets in the postprandial test group were as follows: AUC_{0-t} was ($1.52\times10^4\pm3278.33$) and ($1.54\times10^4\pm3362.99$) h•ng•mL^{-1}, $AUC_{0-\infty}$ was ($1.57\times10^4\pm3474.30$) and ($1.58\times10^4\pm3606.97$) h•ng•mL^{-1}, C_{max} was (1959.67±304.10) and (1966.55±331.73) ng•mL^{-1}, T_{max} was (3.42±1.00) and (3.57±1.26) h, and $t_{1/2}$ was (10.29±1.02) and (10.32±1.07) h, respectively. The geometric mean ratios and 90% confidence intervals for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of test preparation and reference preparation in fasting test group and postprandial test group were in the range of 80.00%~125.00%. The incidence of adverse events in fasting and postprandial tests was 30% (9/30) and 33.3% (10/30), respectively, and no serious adverse events and unintended adverse drug reactions occurred.

Conclusion

The test preparation and the reference preparation of Azilsartan tablets are bioequivalent and safe in Chinese healthy subjects under fasting and postprandial conditions.

1. Introduction

As a kind of chronic disease, hypertension is a major risk factor for human health with high prevalence, high disability rate and heavy disease burden around the world, and it is widely related to cardiovascular and cerebrovascular diseases[1–3]. Angiotensin II receptor blocker (ARB) is the first-line drug for the initial treatment of hypertension, with the characteristics of good antihypertensive effect, few adverse reactions and high patient compliance[4, 5]. Clinical trials have shown that ARB drugs can reduce the proportion of hypertensive patients who develop type 2 diabetes, and can significantly improve the prognosis of patients with high-risk hypertension, heart failure and diabetic nephropathy[6–8]. As a novel ARB drug, Azilsartan is mainly used for the treatment of adult hypertension[9]. As it binds to the angiotensin type II1 receptor (AT_1), which antagonizes angiotensin II and exhibits antihypertensive effects by mainly inhibiting the aldosterone secretion, strong vasoconstriction and other hypertensive effects, and by reducing the peripheral vascular resistance. Compared with the similar antihypertensive drugs Olmesartan and Candesartan, Azilsartan shows stronger antihypertensive effect and better safety[10, 11] with more selective advantage in clinical use.

In this study, the bioequivalence and safety of Azilsartan tablets was evaluated in healthy Chinese subjects between the test preparation provided by Zhaoke Pharmaceutical (Guangzhou) Co., Ltd. and the reference preparation, Azilva®, the original

drug produced by Takeda Pharmaceutical Company Limited in Japan.

2. Materials, subjects and methods

Drugs and preparations Test preparation (T): Azilsartan tablets, strength: 20mg per tablet, batch number: 20180108, produced by Zhaoke Pharmaceutical (Guangzhou) Co., Ltd.; reference preparation (R): Azilsartan tablets (trade name: Azilva®), strength: 20mg per tablet, batch number: AH2101, produced by Takeda Pharmaceutical Company Limited. Azilsartan standard, analyte: Azilsartan, purity: 97%, batch number: 5-SYQ-120-1; internal standard: Azilsartan-d5, purity: 98%, batch number: 5-XDD-19-2, all purchased from Toronto Research Chemicals, Japan.

Instruments LC-30AD high performance liquid chromatograph, Shimadzu, Japan; Triple Quad 5500 mass spectrometer, AB Sciex, USA.

2.2 Subject selection

The trial protocol was approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Bengbu Medical College (ethics approval number: 2018112, the clinical trial registration platform registry number: CTR20191688, clinical trial registration platform website: www.chinadrugtrials.org.cn). All the subjects signed the informed consent. A total of 30 subjects were enrolled for the fasting test, including 19 males and 11 females aged (26.50±6.87) years old with body weight (62.20±8.44) kg and body mass index (BMI) (22.10±2.22) $kg \cdot m^{-2}$. A total of 30 subjects were enrolled for the postprandial test, including 20 males and 10 females aged (30.20±7.83) years old with body weight (64.88±7.56) kg and BMI (22.50±2.05) $kg \cdot m^{-2}$.

Inclusion criteria (1) Healthy Chinese aged 18-45 years old, male or female; (2) Male body weight ≥50.0kg, female body weight ≥45kg, BMI 19.0~26.0kg·m-2 (inclusive); (3) No history of abnormalities in heart, liver, kidney, digestive tract, nervous system and metabolic system, no history of postural hypotension, no history of syncope; (4) Non-lactating women and male subjects who are willing to adopt appropriate contraceptive methods throughout the study period.

Exclusion criteria (1) Abnormality with clinical significance in the vital signs, physical examination, clinical laboratory testing (blood routine, urine routine, blood biochemistry, four indicators for blood transfusion, coagulation routine, female pregnancy testing, drug screening), 12-lead ECG; (2) Subjects with diseases of the nervous system, cardiovascular system, blood and lymphatic system, immune system, digestive system, respiratory system, metabolism and skeletal system, or with any other diseases or physiological conditions that can interfere with the trial results; (3) Subjects (female) are pregnant or breastfeeding; (4) Subjects with a history of allergy to angiotensin receptor antagonists or other antihypertensive drugs or antihypertensive biological agents; (5) Usage of any drug or food with mutual effect with Azilsartan and that can affect its absorption, distribution, metabolism and excretion within one month before screening; (6) Subjects who have donated blood, lost blood (greater than 200ml) or participated in another clinical trial within 3 months prior to screening; (7) History of smoking addiction, alcoholism and drug abuse.

2.3 Grouping, administration and blood sample collection

The study was designed as a single-center, randomized, open-label, single-dose, double-cycle, double-cross clinical trial.

30 subjects were enrolled in both fasting and postprandial tests and randomized to 2 administration sequence groups (T-R or R-T) by 1:1. Each subject underwent 2 cycles of test according to the determined administration sequence with a 7-day wash out period between 2 cycles. The subjects were admitted to the ward one day before administration, and were given test or reference Azilsartan tablet 20mg (1 tablet) with 240ml warm water without food or after high-fat meal in the first cycle (day 1 of the trial) and the second cycle (day 8 of the trial), respectively. Subjects were asked to take the drug after fasting overnight for at least 10 hours for the fasting test, while the recommended high-fat meal was provided 30 minutes before drug administration and the meal would be finished within 30 minutes for the postprandial test. Subjects in both groups were

fasted for 1 hour before and after drug administration, and fasted for 4 hours after drug administration. The lunch and supper were provided after 4 hours and 10 hours, respectively.

At a total of 18 timepoints at 0h (within -1 h) before administration and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours after administration each cycle, 4mL of venous blood samples were collected each time from subjects into the blood collection tube with heparin sodium as anticoagulant. After mixing by gentle inversion, the samples were centrifuged by 2000g, 2-8°C for 10 min. After centrifugation, the plasma was evenly divided into two aliquots, one for assay and one for backup. The exact collection time for each blood sample were recorded in detail. If an venous indwelling needle was used for blood collection, approximately 0.5ml of blood was discarded before each blood collection, and an appropriate amount of normal saline was used to seal the indwelling needle after each blood collection. The blood samples to be tested and the backup blood samples were temporarily stored in a low-temperature refrigerator at -20°C in the Phase I ward, and transferred to an ultra-low temperature refrigerator at -60~-90°C at a later time for testing and analysis.

During the trial, the research physicians and nurses asked the subjects about their subjective feelings and observed the subjects for the occurrence of adverse events. Vital signs were measured for the subjects during the screening period, before admission, 1h before administration, 2h, 6h, 12h, 24h and 48h after administration, and the permissible time window for vital signs monitoring was ±30min. In case of serious adverse events, corresponding emergency measures and treatment would be taken. After the completion of the two-cycle trial, the subjects underwent physical examination and laboratory testing, and those without abnormalities left the ward and the study was completed.

2.4 Assay and sample handling

Chromatographic conditions Chromatographic column: Phenomenex Synergi 4 μm Fusion-RP 80A (50 × 2 mm); mobile phase A: 0.5% formic acid and 10 mmol/L ammonium acetate in water, mobile phase B: 100% acetonitrile; column temperature: 40°C; flow rate: 0.4mL·min^{-1}; injection volume: 5.00 μL. Gradient elution procedure: 0.01~1.3min, 45% B; 1.3-1.5 min, 45%-85% B; 1.5~2.3min, 85% B; 2.3~2.4min, 85%-45% B; 2.4~3.2min, 45% B.

Mass spectrometry conditions Electrospray ion source: positive ion detection; scanning mode: multiple reaction monitoring (MRM); ion source voltage: 5500V; curtain gas: 310.26kpa; collision gas (CAD): 68.95kpa; nebulizer gas (GS1) pressure: 275.79kpa; auxiliary gas (GS2) pressure: 344.74kpa; ion source temperature: 550°C; the ionic reactions used for quantitative analysis were Azilsartan m/z 457.1→233.0 and Azilsartan-d5 m/z 462.2→233.0.

Plasma sample handling After the sample was thawed at room temperature and fully vortexed, 50ul sample was added into a 0.6mL centrifuge tube, 200ul internal standard working solution (100ng/mL of Azilsartan-d5 in acetonitrile) was added to the sample, and centrifuged at 12000g and 4°C for 10min after shaking for 3min. 30ul supernatant was transferred to a 96-well plate containing 270ul of 45% methanol aqueous solution. After shaking the 96-well plate for mixing, the samples were centrifuged at 3000g and 4°C for 10min before placing the 96-well plate into an automatic sampler for injection.

2.5 Methodology investigation and evaluation

Specificity 6 different sources (batches) of human blank plasma were used for assay of blank samples without internal standard and for the addition experiment spiking Azilsartan standard solution and internal standard, respectively, according to the “plasma sample handling” section. The results showed that all the 6 batches of matrix passed the test with the retention times of 1.05min and 1.04min for Azilsartan and the internal standard Azilsartan-d5, respectively. The results indicated that the endogenous substance in blank plasma did not interfere with Azilsartan and internal standard, and there was no mutual interference between Azilsartan and internal standard, showing good specificity of this method. The chromatograms are shown in Figure 1.

Standard curve and lower limit of quantitation(LLOQ) Standard curve samples were taken for 8 mass concentration levels: 3.00, 6.00, 20.0, 90.0, 300, 1000, 2500 and 3000 ng/mL, with 2 replicates for each mass concentration level. The samples were processed according to the “plasma sample handling” section to record the chromatogram for LC/MS-MS analysis. The linear

regression was performed by the least square method with the plasma concentration of Azilsartan as the abscissa (x) and the ratio of Azilsartan peak area to Azilsartan-d5 peak area as the ordinate (y), and the weight factor of $1/x^2$. With the fitting equation of y=ax+b, the linear equation of the standard curve was $y=2.49\times10^{-3}x+3.74\times10^{-4}$ (r=0.9969). The linearity range of Azilsartan plasma concentration was 3.00 ~ 3000 $ng\cdot mL^{-1}$, showing good linear relationship with the lower limit of quantification of 3.00 $ng\cdot mL^{-1}$.

Precision and recovery Control samples were prepared at 5 levels, i.e. LLOQ, low, geometric medium, moderate and high concentration(3.00, 9.00, 100.00, 1500.00, 2400.00 $ng\cdot mL^{-1}$). According to the “plasma sample handling” section, 6 replicates were prepared for each mass concentration, and 3 batches were independently analyzed to calculate the accuracy, precision and absolute recovery within and between batches. The results showed that the relative standard deviations (RSDs) of both within and between batches were < 10%, and the relative error (RE) for accuracy was -2.02%~5.28%, which met the acceptance criteria of biological samples. The relative recovery was the ratio of the concentration of QC sample, calculated from the standard curve of the day, to the amount spiked. The mean recovery rates of Azilsartan were 90.11%, 88.40% and 87.17% respectively in QC samples with low, medium and high concentrations, and the coefficient of variation was no greater than 15%, meeting the requirements for recovery. See Table 1 for details.

Matrix effect The normal blank matrix of 6 different individuals was investigated at the QC levels of low concentration (9.00 ng/mL) and high concentration (2400 ng/mL) for each individual matrix. The matrix factor (MF) for analyte and internal standard was calculated by the ratio of peak area in the presence of matrix (pure solution of normal blank matrix after extraction with the analyte and internal standard added) to the peak area in the absence of matrix (pure solution of ultrapure water, instead of normal blank plasma, after extraction with the analyte and internal standard added). The normalized MF of the internal standard was calculated by dividing the MF of analyte by the MF of internal standard. The mean values of the internal standard normalized matrix factors of the low and high QC concentrations of the normal blank matrix of 6 different individuals were 1.01 and 1.00, respectively, and the coefficient of variation (%CV) was 1.83% and 0.40%, respectively. The total coefficient of variation of the internal standard normalized MF of the low and high concentrations was 1.30%, meeting the acceptance criteria.

Stability The short-term and long-term stability of analyte stock solutions and working solutions, plasma stability, freeze-thaw cycle stability (5 cycles of -75°C freezing/room temperature thawing), sample pretreatment stability (room temperature, 25.5h), sample stability after preparation (8°C, 180h), long-term stability of analyte in biological matrix (-20°C 40.5d, -75°C 40.5d), analyte stability before sample centrifugation (room temperature, 2h) were investigated. The results showed that both Azilsartan and internal standard could maintain stable under the above conditions.

2.6 Statistical analysis

WinNonlin8.2 software was used to analyze the pharmacokinetic parameters with the noncompartmental model for the plasma concentration data of Azilsartan. SAS 9.4 statistical software was used for the descriptive and inferential statistical analysis. After logarithmic transformation of major pharmacokinetic parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$), the mixed effect model was applied for multi-factor analysis of variance and two one-sided t test. The 90% confidence interval of the geometric mean ratio of the main pharmacokinetic parameters of the two drugs was calculated, non-parametric test was conducted for T_{max}, and bioequivalence evaluation was conducted with the equivalence interval set to 80.00% ~ 125.00%.

3. Results

3.1 Subject enrollment and completion

110 and 85 subjects were screened for the fasting and postprandial tests, respectively. A total of 30 subjects were enrolled for the fasting test, including 15 each in the T-R sequence group and the R-T sequence group, they completed all the tests within the two cycles. A total of 30 subjects were enrolled in the postprandial test, including 15 each in the T-R sequence group and

the R-T sequence group. Among them, 1 subject in the T-R group voluntarily withdrew from the study after completing the drug administration and all blood sample collection in the first cycle, while the remaining 29 subjects completed the trial.

3.2 Plasma concentration-time curve

The mean plasma concentration-time curve of subjects after taking test and reference Azilsartan tablet 20mg (1 tablet) orally under fasting and postprandial conditions showed generally consistent change trend of the curve in subjects in the two groups, as shown in Figure 2.

3.3 Pharmacokinetic parameters

The main pharmacokinetic parameters after oral administration of the test and reference Azilsartan tablets in fasting and postprandial tests are shown in Table 2.

3.4 Bioequivalence evaluation

The geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of the test/reference Azilsartan tablets for oral administration under fasting condition in healthy subjects were 89.28%, 95.23% and 95.34%, respectively. The 90% confidence intervals of the geometric mean ratios were 83.54%-95.42%, 92.04%-98.52% and 92.13%-98.66%, respectively, all within the range of 80.00%~125.00%. The *P* values of the two one-sided *t* test results were all less than 0.05. The geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of the test/reference Azilsartan tablets for oral administration under postprandial condition were 99.33%, 98.22% and 98.13%, respectively. The 90% confidence intervals of the geometric mean ratios were 94.66%-104.23%, 95.58%-100.93% and 95.45%-100.89%, respectively, all within the range of 80.00%~125.00%. The *P* values of the two one-sided *t* test results were all less than 0.05. The results indicated bioequivalence between the test and reference Azilsartan tablet 20mg (1 tablet) administered orally under fasting and postprandial conditions.

3.5 Safety evaluation

In the fasting test, 13 adverse events occurred in 9 subjects with the incidence of 30.0%, including hypotension, increased urinary mucus, hematuria, positive urine protein, nausea, headache, vertigo, elevated C-reactive protein, and hyperuricemia. 8 adverse events occurred in 6 subjects administered with the test preparation, including 7 drug-related adverse events in 6 subjects. All the adverse events were classified as grade I except for 2 cases of grade II and 1 case of grade III. 5 adverse events occurred in 4 subjects administered with the reference preparation, including 3 drug-related adverse events in 3 subjects. All the adverse events were classified as grade I.

In the postprandial test, 18 adverse events occurred in 10 subjects with the incidence of 33.3%, including hypotension, elevated direct bilirubin, tonsillitis, reduced high density lipoprotein, elevated C-reactive protein, and hypertriglyceridemia. 9 adverse events occurred in 6 subjects administered with the test preparation, including 7 drug-related adverse events in 5 subjects. All the adverse events were classified as grade I. 9 adverse events occurred in 7 subjects administered with the reference preparation, including 7 drug-related adverse events in 6 subjects. All the adverse events were classified as grade I.

4. Discussion

On February 25, 2011, the US FDA approved its prodrug azilsartan medoxomil tablets (trade name Edarbi®) for the treatment of adult hypertension, and it has shown good efficacy and safety in drug trials for the treatment of primary hypertension in Hong Kong, Taiwan, Thailand and India[12, 13]. Azilsartan tablets were first developed by Takeda Pharmaceutical Company Limited, and approved for marketing in Japan in January 2012 for the treatment of hypertension. Currently, it has not been imported in China. In June 2021, the National Medical Products Administration announced that generic drug Azilsartan tablets of Class 3 were approved for marketing in China, which is of great significance to increase the choices of medication and reduce the long-term economic burden of medication for hypertensive patients in China.

According to the Requirements for Registration Classification and Application Data of Chemical Drugs and the Technical Guidelines for Human Bioequivalence Study of Generic Chemical Drugs with Pharmacokinetic Parameters as the Endpoint Evaluation Indicators[14, 15], the plasma concentration of Azilsartan was determined by LC-MS/MS to evaluate the bioavailability of Azilsartan tablets administered orally to 30 healthy subjects under fasting and postprandial conditions. The geometric mean ratios of pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Azilsartan in plasma for both test preparation and reference preparation were all within 90% confidence interval (80.00%~125.00%), indicating that the test preparation and reference preparations were bioequivalent. At present, there are few literature reports on the pharmacokinetics of Azilsartan tablets in China. In this study, the Azilsartan tablets were administered orally by single dose of 20mg (1 tablet). Compared with oral administration of Azilsartan tablet by single dose of 40mg (1 tablet) reported in China, there was no significant difference in T_{max} and $t_{1/2}$ was slightly shortened in the fasting test; the T_{max} was slightly prolonged and there was no significant difference in $t_{1/2}$ in the postprandial test[16].

A study in China [16] has revealed adverse events of Azilsartan tablets, including hypotension, elevated heart rate, diarrhea, dizziness, asthenia, etc. All adverse events were classified as grade I, and no severe adverse event or serious adverse event occurred. The adverse events in this study included hypotension, dizziness, nausea, elevated C-reactive protein, etc. 2 grade II adverse events occurred in 2 subjects and 1 grade III adverse event occurred in 1 subject. Among them, the specific manifestation of 2 grade II adverse events was hypotension with dizziness. The subjects were asked to rest and drink water and then blood pressure was measured again. The 2 adverse events recovered in relatively short time (18 minutes in 1 case and 52 minutes in the other case). One grade III adverse event was vertigo and panhidrosis, and the subject fell down due to unstable standing. The vertigo disappeared after 8 minutes, which was considered as due to vertigo and sweating caused by decreased blood pressure. All other adverse events were classified as Class I, with no serious adverse events and no obvious safety issues. With the comprehensive observation of the incidence of adverse events and the severity of adverse drug reactions of the test preparation and reference preparation during the study, the dosage of 20mg (1 tablet) of Azilsartan tablet administered orally under fasting and postprandial conditions showed good tolerability and safety in healthy subjects, with similar safety profile between the test and reference preparations.

Therefore, it can be judged that the oral administration of Azilsartan tablets (test preparation) provided by Zhaoke Pharmaceutical (Guangzhou) Co., Ltd. and the original drug (reference preparation) produced by Takeda Pharmaceutical Company Limited in healthy Chinese subjects under fasting and postprandial conditions is bioequivalent, and the test preparation shows good safety, which provides the basis for the consistency evaluation of generic drugs.

Abbreviations

LC-MS/MS liquid chromatographer-tandem mass spectrometry

SAS Statistical Analysis System

AUC_{o-t} area under the plasma concentration-time curve from time 0 to last time of quantifiable concentration

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time 0 extrapolated to infinite time

C_{max} maximum concentration

T_{max} time to reach maximum concentration

$t_{1/2}$ elimination half-life

BMI body mass index

ARB Angiotensin II receptor blocker

AT_1 the angiotensin type II1 receptor

T test group

R reference group

AEs adverse events

DQC Dilution Quality Control

g gram

IS-MF Internal Standard-Matrix Factor

GMQC Geometric Middle Quality Control

HQC High Quality Control

LQC Low Quality Control

MF Matrix Factor

MQC Middle Quality Control

CI Confidence interval

PK pharmaco kinetic parameters

QC Quality control

SS System Suitability

BSA body surface area

Declarations

Acknowledgments

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Authorship contributions statement

XBL contributed to data collection, conducted the analysis, wrote the report, reviewed and revised this manuscript. XRD,XHY, and JX performed research and participated in the acquisition of data. HZ designed the study, wrote the report and revised this manuscript. The authors read and approved the final manuscript.

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Availability of data and materials.

All of the data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

The study passed the review of National Drug Clinical Trial Institution The First Affiliated Hospital of Bengbu Medical College on November 2, 2018, and obtained the approval (No.201800038-02). The written informed consents was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

We confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

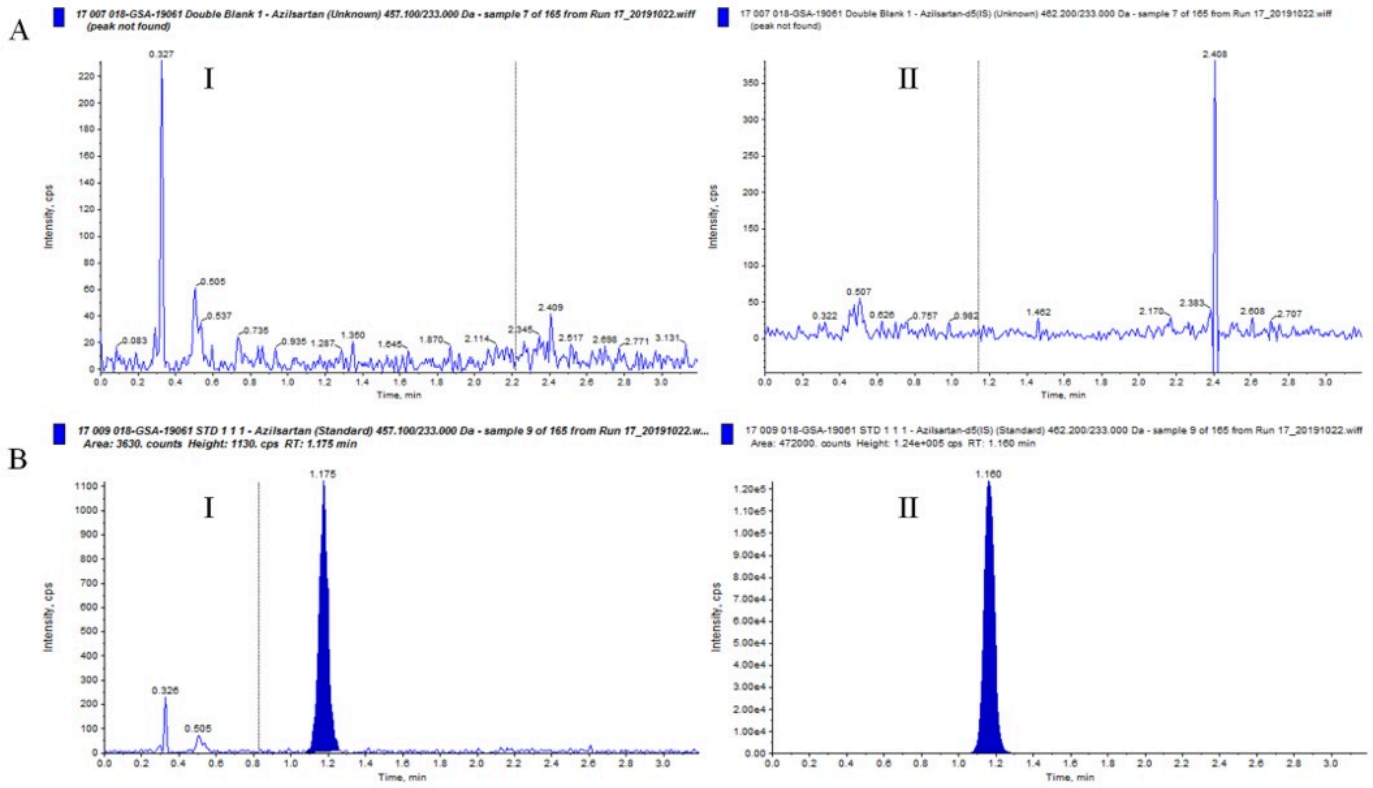

Figure 1

Typical chromatogram of Azilsartan (I) and Azilsartan-d5 (internal standard II) in plasmaA: Blank plasma sample; B:Lower limit of quantitation sample.

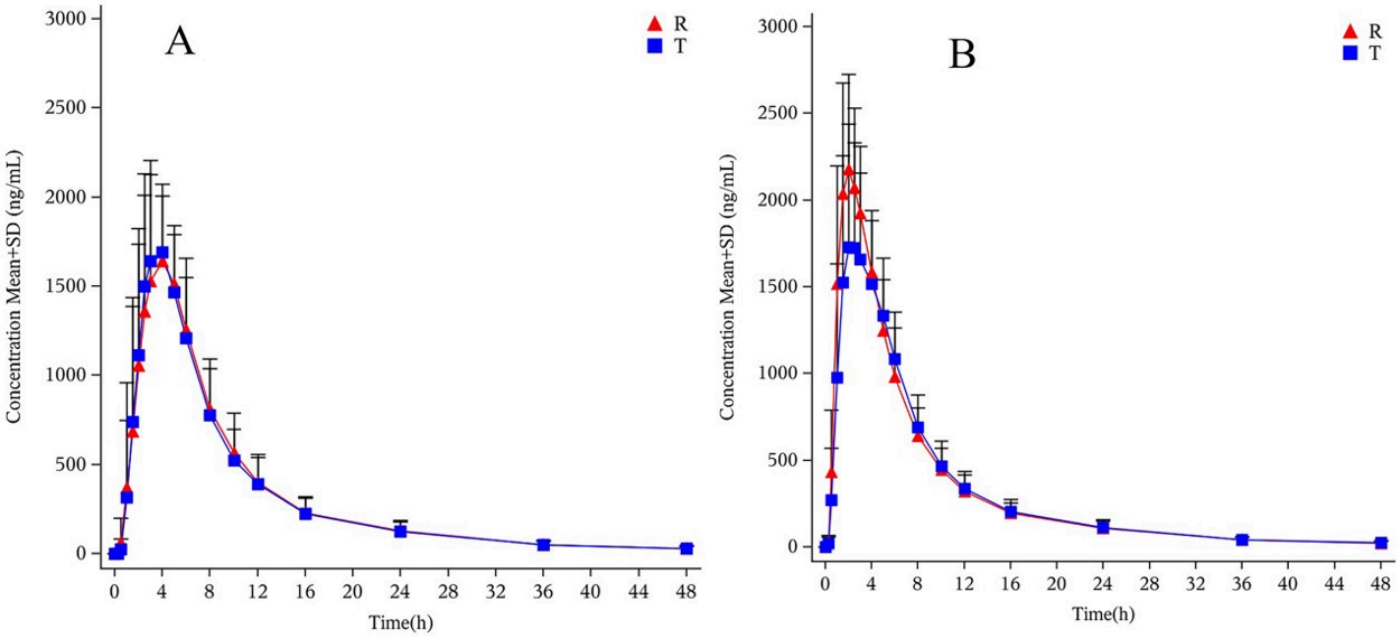

Figure 2

The mean plasma concentration-time curve of test(T) and reference(R) Azilsartan tablets 20mg administered orally under fasting (A) and postprandial conditions (B)

Supplementary Files

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