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A single-dose, four-cycle, fully repetitive crossover bioequivalence of dabigatran etexilate in Chinese

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Abstract

Purpose Among healthy Chinese subjects, two capsules of dabigatran etexilate were tested for bioequivalence.

Method Fifty healthy subjects were recruited for each of the fasting and postprandial trials in a randomized, two-sequence, open-label, four-cycle, fully replicated trial design of a single 150 mg dose of either the test or the reference formulation of dabigatran etexilate capsules in the fasting and postprandial states. The blood concentration of dabigatran at different time points after administration was determined by high-performance liquid chromatography–tandem mass spectrometry (HPLC-MS/MS). The bioequivalence of the two formulations was evaluated by means of the main pharmacokinetic parameters and relative bioavailability.

Results There were 39 males and 11 females in both fasting and postprandial groups. The age, height, weight and BMI of subjects in the fasting group were 19.0–41.0 years old, 148.5–182.0 cm, 46.1–81.0 kg and 19.2–25.7 kg/m^2, respectively, and those in the postprandial group were 18.0–43.0 years old, 145.5–182.5 cm, 45.2–82.0 kg and 19.2–25.9 kg/m^2, respectively. The 90% confidence intervals (CIs) for the geometric mean ratios of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for the total dabigatran in fasting test and reference formulations were 92.41–104.30%, 92.59–104.27% and 93.10–104.27%, respectively. The 90% CIs for the geometric mean ratios of three important parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ pertaining to the total dabigatran in the postprandial test and reference formulations were 97.29–107.77%, 100.43–107.96%, and 100.19–107.40%, respectively. The 90% CIs for the geometric mean ratios of the main pharmacokinetic parameters of the test and reference formulations were in the ranged from 80. 00–125. 00%, and the upper limits of the 90% CIs for the intraindividual variability ratios were ≤2.5. No serious adverse events (SAEs) occurred in the fasting and postprandial groups.

Conclusion The 2 dabigatran etexilate capsules were bioequivalent in both fasting and postprandial states and had favorable safety profile.

Trial registration The enrollment process in this study was finalized on the "Chemical Drug Bioequivalence Trial Record Information Platform." (http://www.chinadrugtrials.org.cn, 04/07/2023, CTR20231968).

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Introduction

Arterial thromboembolic diseases (acute coronary syndromes, atrial fibrillation, strokes, etc.), are among the conditions that cause a high mortality rate in the global population [1, 2]. Globally, the incidence and prevalence of atrial fibrillation (AF) have been steadily increasing [3, 4]. As China is a large country with a large population, the number of people suffering from AF is increasing annually with the aging of the population [5]. Moreover, Chinese patients with AF are characterized by a high prevalence of the disease and a high incidence of stroke, yet the majority of Chinese patients with AF do not receive anticoagulation therapy [6]. In 2010, the U.S. Food and Drug Administration (FDA) formally approved the use of dabigatran for reducing non-valvular atrial fibrillation (NVAF) and stroke risk [7]. Currently, it is recommended by global guidelines as one of the first choices of therapy to prevent stroke or systemic embolism in NVAF patients [8, 9]. A direct thrombin inhibitor known as dabigatran etexilate, alters the hypercoagulable state of the blood by specifically blocking thrombin activity, thus effectively preventing the formation of blood clots and reducing the incidence of thromboembolic diseases such as stroke and heart attack [10–12].

Dabigatran etexilate is the first new oral direct anticoagulant after warfarin, which overcomes the difficulties of low bioavailability of warfarin and the need for drug monitoring, and has been recommended as an alternative to warfarin by the American Guidelines for the Treatment of Atrial Fibrillation [13]. Dabigatran etexilate is rapidly absorbed after oral administration (the maximum C_{max} value reached within 2–4 h), and its absorption is not affected by taking it with food [14, 15]. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial confirmed that dabigatran can be administered at a fixed dose without routine monitoring, and furthermore, that dabigatran ester serves as a comprehensive substitute for warfarin in mitigating the risk of stroke among NVAF patients [16, 17].

The aim of this study compared the differences in absorption rates and extents between the reference formulation (Pradaxa) and the newly developed dabigatran etexilate capsule (150 mg) during fasting and postprandial periods in healthy Chinese individuals to assess their bioequivalence and safety.

Methods

Research drugs

Test preparation (T): dabigatran etexilate capsule, specification: 150 mg per capsule, manufactured and supplied by Henan Topfond Pharmaceutical Co., Ltd (Zhumadian, China), lot number: 22121003X; reference preparation (R): dabigatran etexilate capsule (trade name Pradaxa®, Boehringer Ingelheim International GmbH), specification: 150 mg per capsule, product batch number 105464 (Dispensing lot number E11747).

Subject selection

Research protocols were approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University [approval no. 2023083]. The study strictly adhered to the ethical principles of the Declaration of Helsinki and Good clinical practice (GCP). Prior to involvement, each participant provided written informed consent.

The inclusion criteria were as follows: (1) Chinese male and female subjects aged ≥18 years; (2) body mass index (BMI) for male participants weighing 50 kg or more and female subjects weighing 45 kg or more, with BMI = weight/height^2 (kg/m^2), including borderline values; and (3) Participants who had a comprehensive understanding of the trial's objectives, nature, methodologies, and potential adverse effects, willingly agreed to participate, and signed an informed consent form.

The exclusion criteria were as follows: (1) had a history of clinically significant disorders of the cardiovascular, endocrine, urinary, psychiatric/neurologic, respiratory, hematologic, lymphatic, immune, or musculoskeletal system. (2) Participants who tested positive for hepatitis B virus surface antigen (HBsAg), hepatitis B e antigen (HBeAg), human immunodeficiency virus (HIV), hepatitis C virus antibody (HCV), or treponema pallidum antibody (TP–Ab) were excluded from the study. (3) Those with coagulation disorders, or those with bleeding tendencies (e.g., recurrent gingival bleeding), or those with any condition that has or increases the risk of bleeding (e.g., acute gastritis, gastric and duodenal ulcers, etc.), or those who have had an event that increases the risk of bleeding in the last 6 months, those who have had previous intracranial hemorrhage, gastrointestinal hemorrhage, or violet epilepsy, or those who have had an active pathologic hemorrhage. (4) Women with a previous history of dysfunctional uterine bleeding, including excessive menstrual bleeding, irregular uterine bleeding, or prolonged menstrual cycles (periods > 7 days). (5) Those who used any anticoagulant medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, platelet inhibitors, heparin, fibrinolytic therapies, and other anticoagulants within 1 month prior to screening. (6) History of food, drug allergy or other allergic diseases (asthma, urticaria, eczematous dermatitis, etc.), or known hypersensitivity to any of the ingredients in dabigatran etexilate capsule. (7) Blood donation or significant

blood loss (exceeding 400 mL or 2 units) within three months prior to the test. (8) History of alcoholism. (9) Participants who smoked an average of five or more cigarettes daily in the three months preceding the screening process, or who were unable to commit to abstaining from smoking throughout the duration of the trial. (10) The use of any medication within the previous 14 days, or who has been vaccinated with any vaccine, or who plans to be vaccinated during the trial. (11) Use of any drug that acts on P–gp within 28 days prior to screening. (12) Excessive consumption of tea, coffee or caffeine-rich drinks every day for 3 months before screening. (13) Special dietary requirements, such as the avoidance of low-sodium, low-potassium, or high-calorie diets. (14) Participants with history of surgery within the last three months prior to screening, those who have planned surgeries during the trial period, or any history of surgical procedures that may impact the Pharmacokinetics of the drug. (15) Women who are pregnant or breastfeeding, or who have had a positive pregnancy test prior to the test. (16) Involvement in any other clinical trials within the three months preceding the screening process. (17) Creatinine clearance < 80 mL/min.

Study design

A single-center, single-dose, two-sequence, randomized, open-label, four-period, fully replicated trial design method was used. Screened healthy subjects were randomized into 2 groups: the TRTR group and the RTRT group. Following the collection of a baseline blood sample on the morning of the dosing day, one capsule of 150 mg of each of the subject formulations or the reference formulation was administered 240 mL of warm boiled water in the fasting or postprandial state, and the washout period between doses was 7 days. The subjects in the postprandial trial ate a high-fat meal totaling approximately 950 kcal.

The subjects were exposed to fasting conditions for 0 h before (within 60 min prior to dosing) and 0.25, 0.5, 0.75, 1, 1.33 (80 min), 1.67 (100 min), 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, and 48 h (a total of 18 points) per cycle of dosing. Postprandial conditions 0 h before (within 60 min before) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 24, and 48 h after each cycle of the drug (18 points in total). Approximately 4 mL of venous blood was collected from each sample in precooled EDTA-K2 anticoagulated blood collection tubes and centrifuged at 1700*g* for 10 min at 4 °C (2 ~ 8 °C). All the samples were centrifuged and then stored in a refrigerator maintained at or below −60 ℃ for a period of 2 h prior to analysis. The plasma concentration of total dabigatran was determined via by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) after oral administration of the test preparation or reference preparation to the subjects [18, 19]. The linear range of the method for total dabigatran plasma concentration was 1.000–300.0 ng/mL, and the lowest limit of quantification was 1.000 ng/mL.

Safety assessment

The subjects' vital signs (including pulse, blood pressure, and forehead temperature) were measured within 2 h before and 2, 4, 8, 24, and 48 h after each cycle of drug administration, with an allowable time window of ±1 h for vital sign measurements, and reference values ranging from (including borderline values): systolic blood pressure: 85–139 mmHg; diastolic blood pressure: 55–89 mmHg; pulse: 50–100 beats/minute; forehead temperature: pulse: 50–100 beats/min; Frontal temperature: 35.5–37.3 °C. Vital signs, 12-lead ECG, blood counts, and coagulation are required at the end of the second cycle of sampling. After the final cycle of sampling, the subjects must undergo a physical examination, assessment of vital signs, a 12-lead electrocardiogram, and various laboratory tests. During the study period, the subjects were observed and questioned about their subjective feelings and possible adverse reactions and events that might have occurred during the trial.

Pharmacokinetic analysis and statistical analysis

Non-atrial modeling was performed via Phoenix WinNonlin (Version No. 8.2, Pharsight Corporation, California, USA) to calculate the pharmacokinetic parameters for each subject, including the bracketed peak concentration (C_{max}), the area under the blood concentration time curve (AUC_{0-t} and $AUC_{0-\infty}$), the time to peak (T_{max}), the elimination half-life ($t_{1/2}$), and the elimination rate constant (λ).

Plasma free and total dabigatran PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were used as the main evaluation metrics for bioequivalence assessment. Using the average bioequivalence (ABE) method, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were analyzed for individual variability after logarithmic transformation using analysis of variance (ANOVA) in a repeated crossover trial design with dosing sequence, dosing period, and formulation factors as fixed effects and formulation factors across subjects as random effects, taking into account repeated measurements of the formulation within a subject (i.e., repeated dosing of T and R), and calculating the geometric mean ratio (GMR) and its 90% confidence interval (CI). The 90% CIs for the intraindividual standard deviation ratios were calculated by logarithmic transformation of the variance components and Fieller's theorem. The specific steps are as follows: First, intraindividual variance components (σ^2_{WT} and σ^2_{WR}) were calculated for fasting and postprandial states. Second, the intra-individual standard deviation ratios (σ_{WT}/σ_{WR}) were log-transformed and

their standard errors (SE) were calculated. Finally, based on the log-transformed values and their SEs, 90% confidence intervals were calculated and converted back to the original scale.

A subject formulation is judged to be bioequivalent to a reference formulation when the 90% confidence interval for the ratio of the geometric means of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for the subject and reference formulations passes the average bioequivalence limit of 80.00% to 125.00%, and the upper limit of the 90% CI for the ratio of the intraindividual standard deviations of the subject and reference formulations is less than or equal to 2.5.

Results

Baseline demographics

According to the criteria for inclusion and exclusion, a total of 100 subjects were ultimately included in the analysis, including 50 in the fasting group and 50 in the postprandial group. Table 1 presents baseline characteristics, encompassing demographic information, height, weight, and body mass index (BMI). There were 39 males and 11 females in both fasting and postprandial groups. The age, height, weight and BMI of subjects in the fasting group were 19.0–41.0 years old, 148.5–182.0 cm, 46.1–81.0 kg and 19.2–25.7 kg/m^2, respectively, and those in the postprandial group were 18.0–43.0 years old, 145.5–182.5 cm, 45.2–82.0 kg and 19.2–25.9 kg/m^2, respectively.

Two subjects in the fasting group withdrew from the trial at the end of the first cycle during the washout period and the fourth cycle, one subject experienced an adverse event (AE) on the second day of dosing in the second cycle, and the investigator judged that withdrawal from the study would be in the best interest of the subject to withdraw from the trial. The remaining 47 subjects completed all cycles. One subject in the postprandial group withdrew from the trial on Cycle 4, another subject experienced an AE on the day of Cycle 4 administration, and the investigator judged that withdrawal from the study would be in the best interest of the subject to withdraw from the trial. The remaining 48 subjects completed the trial.

Table 1 Baseline characteristics of the subjects in the fasting and postprandial cohorts

	Fasting	Postprandial
Male	39	39
Female	11	11
Age	25.62 ± 4.27	25.12 ± 5.40
BMI	21.54 ± 1.60	22.09 ± 1.73
Height	164.59 ± 7.92	165.52 ± 8.41
Weight	58.52 ± 7.49	60.74 ± 8.37

Pharmacokinetics

Figure 1 depicts the plasma concentration-time profile and the semilogarithmic plasma concentration-time curves of free dabigatran after a single oral dose of 150 mg of dabigatran etexilate capsule, under fasting conditions (A) and postprandial conditions (B).

Figure 2 depicts the plasma concentration-time profile and the semilogarithmic plasma concentration-time curves of total dabigatran after a single oral dose of 150 mg of dabigatran etexilate capsule, under fasting conditions (A) and postprandial conditions (B).

The pharmacokinetic parameters and bioequivalence analysis of a single oral dose of dabigatran applied to the capsules of the subjects are shown in Tables 2 and 3.

As shown in the Figs. 1 and 2, the C_{max} and AUC of dabigatran were affected by food. As shown in Table

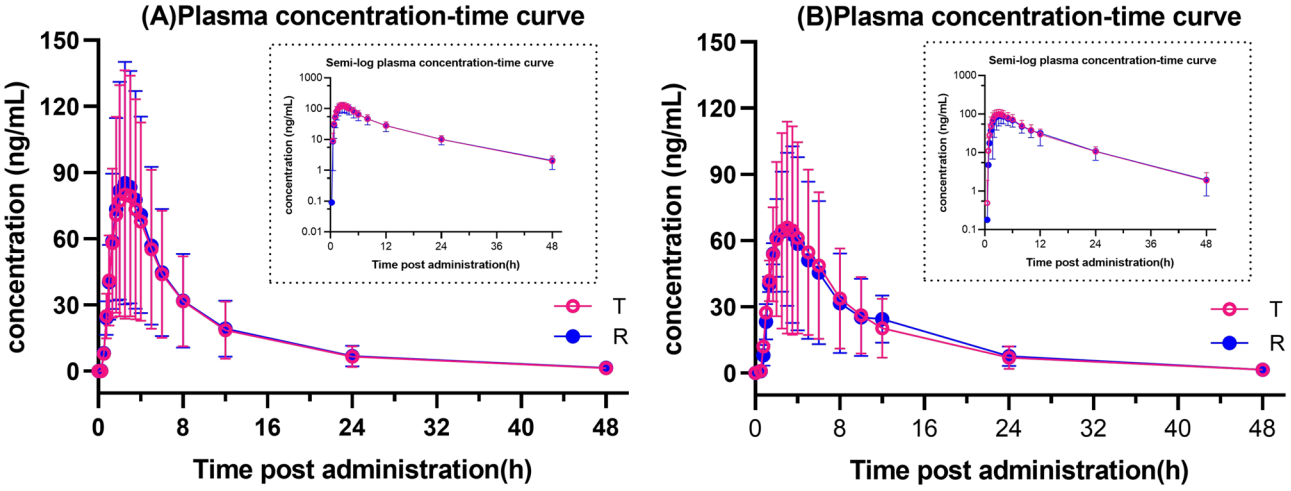

Fig. 1 Fasting (**A**) and postprandial (**B**) plasma free dabigatran concentration-time profiles. A graphical depiction showcasing the average plasma concentration of free dabigatran over time, in both the fasting (**A**) and postprandial (**B**) states, in healthy Chinese participants after the administration of both the test (T) and reference (R) dabigatran etexilate capsules. The inset is the corresponding semi-log plasma concentration-time plot. Each error bar represents the standard deviation (SD)

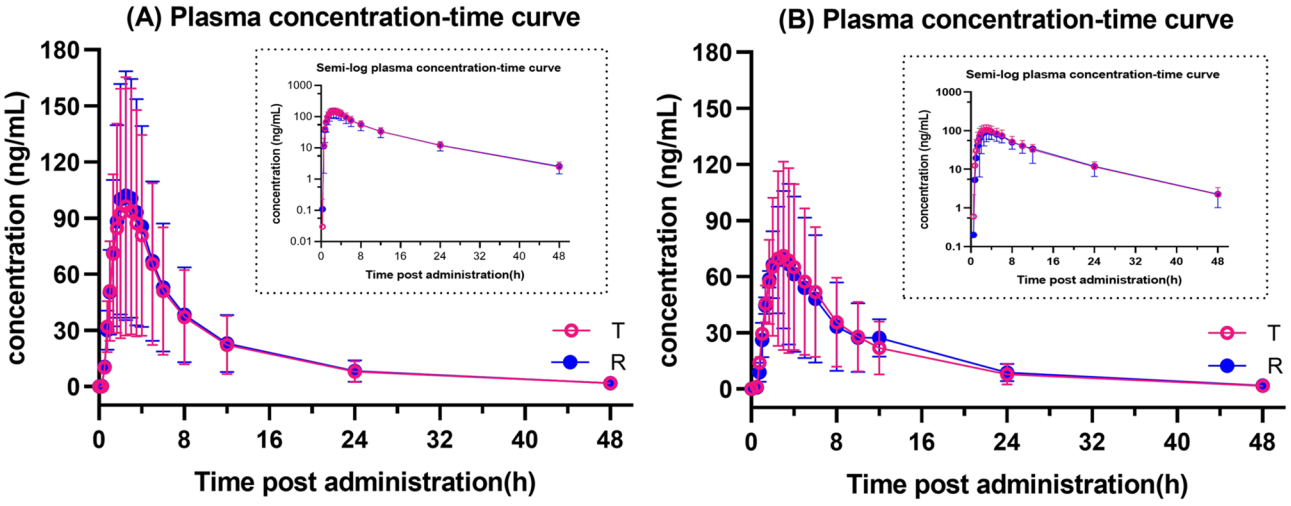

Fig. 2 Fasting (**A**) and postprandial (**B**) plasma total dabigatran concentration-time profiles. A graphical depiction comparing the average plasma concentration of total dabigatran over time, in healthy Chinese subjects under both fasting (**A**) and postprandial (**B**) conditions. The inset is the corresponding semi-log plasma concentration-time plot. Each error bar represents the standard deviation (SD)

Table 2 Pharmacokinetic parameters of dabigatran etexilate capsules after oral administration of the test and reference formulations to subjects

Parameters	Total dabigatran		Free dabigatran	
	Test (T)	Reference (R)	Test (T)	Reference (R)
Fasting (Mean ± SD)				
C_{max}(ng/mL)	156 ± 47.8	162 ± 56.7	129 ± 42.3	133 ± 48.1
T_{max}*	2.50 (1.33, 4.00)	2.50 (1.33, 5.00)	2.50 (1.33, 4.00)	2.50 (1.33, 5.00)
AUC_{0-t}(ng·h/mL)	1343 ± 427	1376 ± 458	1119 ± 370	1138 ± 389
$AUC_{0-\infty}$(ng·h/mL)	1382 ± 430	1415 ± 469	1152 ± 369	1172 ± 393
$t_{1/2}$	9.63 ± 1.16	9.77 ± 1.66	9.49 ± 1.29	9.57 ± 1.52
$\lambda_z(h^{-1})$	0.0700 ± 0.0100	0.0700 ± 0.0100	0.0700 ± 0.0100	0.0700 ± 0.0100
$AUC_{\_\%Extrap}$	3.20 ± 2.33	2.96 ± 1.93	3.41 ± 2.75	3.26 ± 2.23
Postprandial (Mean ± SD)				
C_{max}(ng/mL)	119 ± 37.5	118 ± 39.8	112 ± 33.0	110 ± 35.8
T_{max}*	4.00 (1.50, 5.50)	4.00 (1.50, 12.0)	4.00 (1.50, 6.00)	4.50 (1.50, 12.0)
AUC_{0-t}(ng·h/mL)	1112 ± 349	1079 ± 339	1030 ± 322	998 ± 307
$AUC_{0-\infty}$(ng·h/mL)	1149 ± 354	1098 ± 329	1068 ± 320	1020 ± 303
$t_{1/2}$	9.41 ± 1.54	9.39 ± 1.38	9.24 ± 1.64	9.09 ± 1.42
$\lambda_z(h^{-1})$	0.0800 ± 0.0100	0.0800 ± 0.0100	0.0800 ± 0.0100	0.0800 ± 0.0100
$AUC_{\%Extrap}$	3.44 ± 2.05	3.52 ± 2.30	3.97 ± 2.91	3.86 ± 2.83

C_{max} peak plasma concentration, T_{max} time to reach the peak plasma concentration, AUC_{0-t} Area under the plasma concentration-time curve from time zero to time t, $AUC_{0-\infty}$ Area under the curve from time 0 extrapolated to infinity, $t_{1/2}$ elimination half-life, λ_z elimination rate constant, $AUC_{\_\%Extrap}$ Greater than 20% extrapolation.
*T_{max} is expressed as the median (min, max)

2, after fasting oral administration of the test and reference formulations, the C_{max} values of free dabigatran were 129 ± 42.3 ng/mL and 133 ± 48.1 ng/mL, the AUC_{0-t} values were 1119 ± 370 ng·h/mL and 1138 ± 389 ng·h/ mL, the $AUC_{0-\infty}$ values were 1152 ± 369 ng·h/ mL and 1172 ± 393 ng·h/mL, respectively, and the T_{max} values were 2.50 (1.33, 4.00) h and 2.50 (1.33, 5.00) h, respectively. The C_{max} values of total dabigatran were 156 ± 47.8 ng/mL and 162 ± 56.7 ng/mL, and the AUC_{0-t} values were 1343 ± 427 ng·h/mL and 1376 ± 458 ng·h/ mL. The $AUC_{0-\infty}$ values were 1382 ± 430 ng·h/mL and 1415 ± 469 ng·h/mL, and the T_{max} values were 2.50 (1.33, 4.00) h and 2.50 (1.33, 5.00) h, respectively. After postprandial oral administration of the test and reference formulations, the C_{max} values of free dabigatran were 112 ± 33.0 ng/mL and 110 ± 35.8 ng/mL, and the AUC_{0-t} values were 1030 ± 322 ng·h/mL and 998 ± 307 ng·h/ mL, respectively. The $AUC_{0-\infty}$ values were 1068 ± 320 ng·h/mL and 1020 ± 303 ng·h/mL, respectively, and the T_{max} values were 4.00 (1.50, 6.00) h and 4.50 (1.50, 12.0) h, respectively. The C_{max} values of total dabigatran were 119 ± 37.5 ng/mL and 118 ± 39.8 ng/mL, the

Table 3 Bioequivalence of the main pharmacokinetic parameters of dabigatran in subjects after oral administration of the test and the reference

Parameters	Free dabigatran				Total dabigatran			
	T/R GMR (%)	90%CIs	σ_{WT}/σ_{WR}	90% CIs	T/R GMR (%)	90%CIs	σ_{WT}/σ_{WR}	90% CIs
Fasting								
C_{max} (ng/mL)	98.1	92.4–104	1.15	0.899–1.47	98.2	92.4–104	1.08	0.845–1.38
AUC_{0-t} (h*ng/mL)	98.9	93.2–105	1.33	1.04–1.71	98.3	92.6–104	1.32	1.03–1.68
$AUC_{0-\infty}$ (h*ng/mL)	99.1	93.6–105	1.32	1.03–1.69	98.5	93.1–104	1.30	1.02–1.67
Postprandial								
C_{max} (ng/mL)	103	98.3–108	0.954	0.746–1.22	102	97.3–108	0.963	0.753–1.23
AUC_{0-t} (h*ng/mL)	104	100–108	1.14	0.890–1.46	104	100–108	1.09	0.849–1.39
$AUC_{0-\infty}$ (h*ng/mL)	104	100–107	1.09	0.856–1.40	104	100–107	1.09	0.853–1.40

C_{max} peak plasma concentration, *AUC_{0-t}* Area under the plasma concentration-time curve from time zero to time t, *$AUC_{0-\infty}$* area under the curve from time 0 extrapolated to infinity, *GMR* geometric mean ratio, *CIs* confidence intervals, *σ_{WT}* intra-individual variability of test product, *σ_{WR}* intra-individual variability of reference product

Table 4 Coagulation parameters under fasting and postprandial conditions

Pharmacodynamic parameters	Screening (Mean ± SD)	Second periodicity (Mean ± SD)	Fourth periodicity (Mean ± SD)
Fasting	**(Subjects with tests, n = 50)**		**(Subjects with tests, n = 48)**
PT (s)	13.01 ± 0.490	12.89 ± 0.475	13.07 ± 0.488
PTA (%)	101.7 ± 7.960	104.4 ± 8.741	101.2 ± 8.167
APTT (s)	36.22 ± 3.090	36.71 ± 3.947	36.61 ± 3.352
TT (s)	17.71 ± 0.880	19.58 ± 1.976	20.73 ± 2.099
Postprandial	**(Subjects with tests, n = 49)**	**(Subjects with tests, n = 50)**	
PT (s)	12.62 ± 0.570	13.14 ± 0.504	12.82 ± 0.479
PTA (%)	108.9 ± 10.58	100.2 ± 8.297	105.5 ± 8.808
APTT (s)	36.25 ± 2.860	36.06 ± 2.660	36.22 ± 2.746
TT (s)	17.63 ± 0.940	20.78 ± 2.490	21.30 ± 2.537

PTA prothrombin time activity (%), *TT* thrombin time (s), *PT* prothrombin time (s), *APTT* activated partial thromboplastin time (s)

AUC_{0-t} values were 1112 ± 349 ng·h/mL and 1079 ± 339 ng·h/mL, the $AUC_{0-\infty}$ values were 1149 ± 354 ng·h/mL and 1098 ± 329 ng·h/mL, respectively, and the T_{max} values were 4.00 (1.50, 5.50) h and 4.00 (1.50, 12.0) h, respectively.

As shown in Table 3, the geometric mean ratios 90% confidence intervals (CIs) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for free and total dabigatran in fasted and postprandial states for the test and reference formulation were all within the bioequivalence range (80.00~125.00%). The upper 90% CIs of the intraindividual standard deviation ratios for free and total dabigatran in the fasting group were as follows: C_{max} values were 1.47 and 1.38, respectively; AUC_{0-t} values were 1.71 and 1.68, respectively; and $AUC_{0-\infty}$ values were 1.69 and 1.67, respectively. The upper 90% CIs of the intraindividual standard deviation ratios for free and total dabigatran in the postprandial group were as follows: C_{max} values were 1.22 and 1.23, respectively; AUC_{0-t} values were 1.46 and 1.39, respectively; and $AUC_{0-\infty}$ values were 1.40 and 1.40, respectively. The upper 90% CIs of the intraindividual standard deviation ratios σ_{wT}/σ_{wR} were less than 2.5 for C_{max}, AUC for both free and total dabigatran.

Pharmacodynamics

In our study, a total of coagulation parameters including prothrombin time (PT), prothrombin time activity (PTA), activated partial thromboplastin time (APTT), and thrombin time (TT) were examined at the time of screening, at the end of the second cycle and at the end of the fourth cycle of sampling. Table 4 shows the coagulation parameters under fasting and postprandial conditions.

After dabigatran etexilate administration, the values of TT increased more significantly, both fasting and postprandial, whereas other coagulation monitoring parameters did not change significantly between the 2 groups.

Safety

Throughout the study, all the subjects underwent relevant safety checks before and after dosing, and no serious adverse events (SAEs) occurred during the trial in either the fasting or postprandial groups. The results of the AEs in both states are shown in Table 5. A total of 14 AEs occurred in 10 subjects during the course of the trial in the fasting group (8 events in the T group and 6 events in the R group). There were 8 AEs in 7 subjects in Group T, with an incidence of 14.3%, and 6 AEs in 4 subjects in Group R, with an incidence of 8.0%. A total of 19 AEs occurred in 11 subjects during the trial in the postprandial group (5 events in the T group and 14 events in the R group). There were 5 AEs in 5 subjects in Group T, with an incidence of 10.0%, and 14 AEs in 6 subjects in Group R, with an incidence of 12.0%. Both the subject and reference formulations of dabigatran etexilate capsules exhibited a favorable safety profile.

Table 5 Subjects with adverse events after oral administration of 150 mg dabigatran during the study

AE	Fasting group (N = 47)				Postprandial group (N = 48)			
	nAE	T	nAE	R	nAE	T	nAE	R
Vascular and Lymphatic Vessel Diseases								
Nasal bleeding	2	1	0	0	2	1	2	1
Hypotension	1	1	0	0	0	0	0	0
Laboratory Results								
Prolonged thrombin time	2	1	0	0	4	2	12	6
Increased LDL-cholesterol	2	1	0	0	0	0	0	0
Increased blood cholesterol	2	1	0	0	0	0	0	0
Decreased blood leucocyte count	2	1	4	2	0	0	0	0
Increased blood basophil percentage	0	0	2	1	0	0	0	0
Decreased neu-trophil absolute value	0	0	2	1	0	0	0	0
Blood uric acid level increase	0	0	2	1	0	0	0	0
Increase of serum triglyceride	0	0	0	0	0	0	2	1
Decreased blood phosphorus	0	0	0	0	0	0	2	1
Blood glucose reduction	2	1	0	0	0	0	0	0
Gastrointestinal disorders								
Diarrhea	2	1	0	0	0	0	0	0
Nausea	0	0	0	0	2	1	4	2
Vomiting	0	0	0	0	0	0	4	2
Others								
Urethritis	0	0	1	1	0	0	2	1
Sinus bradycardia	0	0	0	0	2	1	0	0

In the fasting group, 47 subjects completed the trial (24 in the TRTR group and 23 in the RTRT group). Among them, one subject in the RTRT group did not take the medication in cycles 2, 3, and 4, and another subject missed the medication in cycle 4. Additionally, one subject in the TRTR group did not take the medication in the third and fourth cycles. In the postprandial group, all 48 subjects completed the trial (24 in the TRTR group and 24 in the RTRT group), except for one subject in the RTRT group who was not dosed in the fourth cycle

Discussion

In this trial, a fasting group and a postprandial group consisted of 50 subjects each, and the blood concentrations of free dabigatran and total dabigatran were determined under fasting and feeding conditions in healthy Chinese volunteers to evaluate the pharmacokinetics and bioequivalence of dabigatran. The 90% CIs for the key pharmacokinetic (PK) parameters C_{max} and AUC ranged from 80.00–125.00%, there was no greater than 2.5 at the upper limit of the 90% CI for σ_{WT}/σ_{WR}, and there were no differences in the pharmacokinetic profiles or safety profiles of test and reference formulations during fasting or postprandial periods. Therefore, 150 mg of dabigatran etexilate capsules (test formulation, Manufactured and supplied by Henan Topfond Pharmaceutical Co., Ltd (Zhumadian, China)) and 150 mg of dabigatran etexilate capsules (reference formulation, trade name Pradaxa®, Boehringer Ingelheim International GmbH) were bioequivalent. The dabigatran etexilate capsule test formulation and the reference formulation in this study were well tolerated and safe with no SAEs.

Dabigatran directly inhibits thrombin, and therefore the assay TT provides the most sensitive and direct reflection of the anticoagulant activity of dabigatran. The coagulation parameters after dabigatran administration in this study were measured at lower plasma concentrations, so only the TT values changed significantly before and after administration. APTT was essentially unchanged at low concentrations of dabigatran, as were PT and PTA values.

Approximately 2.5 h and 4 h were the median T_{max} values in the present study, both under fasting and postprandial conditions, respectively, which are similar to previous reports in Chinese populations [18, 20], and Caucasians [21, 22]. The C_{max} and $AUC_{0-\infty}$ of total dabigatran in this study exhibited approximately 20–30% higher levels compared to Caucasian subjects under fasting conditions, and approximately 10–20% higher levels under postprandial conditions [21]. This difference between Chinese and Caucasian individuals may be due to body weight, serum creatinine and genetic variation [18, 23, 24].

The present study investigated and compared the changes in key PK parameters of the test formulation of dabigatran with those of the reference formulation in the fasted and postprandial states. Compared with those of fasting subjects, the main PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of free and total dabigatran decreased after the participants consumed a high-fat meal. Free dabigatran decreased by 12.91%, 7.92%, and 7.29% for the subject formulation and by 17.20%, 12.25%, and 12.95% for the reference

formulation, respectively. The total dabigatran concentration decreased by 23.76%, 17.21%, and 16.84% for the test formulation and 27.22%, 21.57%, and 22.43% for the reference formulation, respectively. There was a decrease in the C_{max} and AUC when dabigatran was ingested with food, which is similar to the findings of previous studies [21, 25]. Moreover, dabigatran T_{max} was prolonged from 2.5 to 4 h after a high-fat meal consumption. An investigation of the effects of dabigatran exposure, revealed that female gender and lower CrCl were associated with increased exposure to dabigatran [21]. In contrast, there were no subjects whose CrCL was below normal in our study, and females accounted for only 22% of the total number of subjects. This suggests that when dabigatran is ingested with food, food intake only delays the absorption of dabigatran [18, 20, 21] and has a lesser effect on the extent of absorption, although a high-fat breakfast may alter the C_{max} and AUC.

We exhaustively collected AEs that occurred after administration of the test drug and the reference drug during the trial. During the course of the study, a total of 13 AEs occurred in the subject formulation and 19 AEs occurred in the reference formulation, all of which were determined to be mild and no serious AEs occurred. After follow-up, most of the subjects were cured. Overall, testing and referencing dabigatran ester healthy Chinese volunteers were safe by this drug when fasting and postprandial.

Although this study was conducted in healthy subjects, the mechanism of action of the drug was consistent across healthy populations and patients. In addition, this study was an open-label trial designed to assess the bioequivalence of dabigatran in healthy subjects. Although dabigatran is mainly used in patients with cardiovascular disease, atrial fibrillation, or stroke, and the pharmacokinetic and pharmacodynamic properties of the healthy population differ from those of patients, the pharmacokinetic parameters of healthy subjects are more stable and can more clearly reflect the absorption, distribution, metabolism, and excretion characteristics of the drug, thus providing reliable baseline data for subsequent patient studies to validate the efficacy and safety of dabigatran in specific disease states.

Conclusion

The pharmacokinetic characteristics and safety of the 150 mg dabigatran etexilate capsule test formulation and the reference formulation are similar under fasting and postprandial conditions, indicating their bioequivalence. Food intake significantly delayed the absorption of dabigatran and altered its C_{max} and AUC to some extent but had a lesser effect on the extent of absorption.

Abbreviations

AE	Adverse event
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to time
$AUC_{0-\infty}$	Area under the curve from time 0 extrapolated to infinity
$AUC_{\_\%Extrap}$	Greater than 20% extrapolation
BMI	Body mass index
CI	Confidence interval
C_{max}	Peak plasma concentration
ECG	Electrocardiogram
HPLC-MS/MS	High-performance liquid chromatography–tandem mass spectrometry
PK	Pharmacokinetic
SAE	Serious adverse event
T_{max}	Time to reach the peak plasma concentration
$t_{1/2}$	Elimination half-life
λ_z	Elimination rate constant

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Author contributions

JC, ZY designed and conceived the study; QL, DY analyzed the data, YW, SL designed and planned the study, YH presented the idea, and supervised the work and findings of the study; ZY, and wrote the original manuscript; XZ, LC, Y Zhou, CC and CZ conceived the study; Y Zeng, YX and QZ pretreatment of blood samples; CC, NL, PD and LL collected and processed the trial data. All the authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Research protocols were reviewed and approved by the Ethics Committee of the Affiliated Hospital of Guizhou Medical University [The ethical approval number is 2023083]. Written informed consent was obtained from each subject before participation.

Consent for publication

Written consent was clearly and exhaustively obtained from the subjects during the informed consent process, and all subjects' personal information was ensured not to be disclosed or publicized.

Competing interests

The authors declare no competing interests.

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References

1. Gao Q, Zhen K, Xia L, et al. Assessment of the effect on thromboprophylaxis with multifaceted quality improvement intervention based on clinical decision support system in hospitalized patients: a pilot study. J Clin Med. 2022;11(17):4997.
2. Lirong T, Minmin X, Manqiu Y, et al. Performance evaluation of thrombus molecular markers thrombomodulin, thrombin-antithrombin complex, plasmin-α2-plasmin inhibitor complex, and tissue plasminogen activator-inhibitor complex by a chemiluminescence analyzer. Hippokratia 2022;26:78–82.
3. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation. Circulation 2014;129:837–47.
4. Danelich IM, Reed BN, Hollis IB, et al. Clinical update on the management of atrial fibrillation. Pharmacotherapy 2013;33:422–46.
5. Shi S, Tang Y, Zhao Q, et al. Prevalence and risk of atrial fibrillation in China: a national cross-sectional epidemiological study. Lancet Reg Health West Pac. 2022;23:100439.
6. Zhou Z, Hu D. An epidemiological study on the prevalence of atrial fibrillation in the Chinese population of mainland China. J Epidemiol. 2008;18(5):209–16.
7. Kirley K, Qato DM, Kornfield R, et al. National trends in oral anticoagulant use in the United States, 2007 to 2011. Circ Cardiovasc Qual Outcomes 2012;5:615–21.
8. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation 2019;140:e125–e51.
9. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373–498.
10. Benamouzig R, Guenoun M, Deutsch D, et al. Review article: gastrointestinal bleeding risk with direct oral anticoagulants. Cardiovasc Drugs Ther 2022;36:973–89.
11. Vidal J, DePalma R, Forouzan L. Reversal of Dabigatran bleeding and coagulopathy using idarucizumab in a patient with acute kidney injury. P T. 2018;43(12):748–49.
12. Calkins H, Willems S, Gerstenfeld EP, et al. Uninterrupted Dabigatran versus Warfarin for ablation in atrial fibrillation. New Engl J Med 2017;376:1627–36.
13. Fan P, Gao Y, Zheng M, et al. Recent progress and market analysis of anticoagulant drugs. J Thoracic Dis 2018;10:2011–25.
14. Stangier J, Stähle H, Rathgen K, et al. Pharmacokinetics and pharmacodynamics of the direct oral thrombin inhibitor Dabigatran in healthy elderly subjects. Clin Pharmacokinet 2008;47:47–59.
15. Garnock-Jones KP. Spotlight on Dabigatran etexilate in the prevention of stroke and systemic embolism in patients with atrial fibrillation. Drugs Aging. 2011;28(5):415–19.
16. Liesenfeld K-H, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE–LY trial. J Thromb Haemost 2011;9(11):2168–75.
17. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. New Engl J Med 2009;361:1139–51.
18. Li X, Liu L, Xu B, et al. Bioequivalence and pharmacodynamics of a generic dabigatran etexilate capsule in healthy Chinese subjects under fasting and fed conditions. Pharmacol Res Perspect 2020;8(2):e00593.
19. Brückner L, Beyer-Westendorf J, Tiebel O, et al. Development and validation of an analytical method for the determination of direct oral anticoagulants (DOAC) and the direct thrombin-inhibitor argatroban by HPLC-MS/MS. J Thromb Thrombolysis 2022;53:777–87.
20. Liu Y, Yang C, Qi W, et al. The Impact of ABCB1 and CES1 polymorphisms on Dabigatran pharmacokinetics in healthy Chinese subjects. Pharmgenomics Pers Med. 2021;14:477–85.
21. Stangier J, Eriksson BI, Dahl OE, et al. Pharmacokinetic profile of the oral direct thrombin inhibitor dabigatran etexilate in healthy volunteers and patients undergoing total hip replacement. J Clin Pharmacol 2005;45:555–63.
22. Härtter S, Sennewald R, Nehmiz G, et al. Oral bioavailability of dabigatran etexilate (Pradaxa(®)) after co-medication with verapamil in healthy subjects. Br J Clin Pharmacol 2013;75:1053–62.
23. Lin SY, Tang SC, Kuo CH, et al. Factors affecting serum concentration of dabigatran in Asian patients with non-valvular atrial fibrillation. J Formos Med Assoc Taiwan Yi Zhi 2019;118:1154–60.
24. Paré G, Eriksson N, Lehr T, et al. Genetic determinants of dabigatran plasma levels and their relation to bleeding. Circulation 2013;127:1404–12.
25. Alban S. Pharmacological strategies for inhibition of thrombin activity. Curr Pharm Des. 2008;14(12):1152–75.

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