ORIGINAL RESEARCH ARTICLE

Pharmacokinetics and Safety of Dabigatran Etexilate after Single and Multiple Oral Doses in Healthy Chinese Subjects

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Abstract

Background and Objective Dabigatran etexilate is a non-vitamin K antagonist oral anticoagulant (NOAC) that is used to prevent stroke and systemic embolism in adults with nonvalvular atrial fibrillation (NVAF) and one or more risk factors. Pharmacokinetic data on this anticoagulant in Chinese subjects are limited. This study aimed to provide further information on the pharmacokinetic profile of dabigatran in healthy Chinese subjects, together with its safety profile.

Methods This was an open-label, single-centre, phase I study. Subjects were randomized into 110 and 150 mg dabigatran etexilate treatment groups. Each subject received 7 days of treatment: a single dose on day 1, no dose on days 2–3, and then multiple doses on days 4–10. Blood samples were collected to analyze the pharmacokinetic profile of dabigatran. All adverse events (AEs) were recorded. Routine clinical laboratory tests, a physical examination, vital signs, and 12-lead electrocardiogram (ECG) measurements were performed.

Results A total of 28 subjects (14 males and 14 females) were randomized in this trial. The plasma concentration of total dabigatran reached its maximum measured concentration at a median time of 3–4 h from the dose of interest (either the initial single dose on day 1 or the final dose on day 10) under fed conditions, and declined with an elimination half-life of 10.7–10.9 h following the dose of interest. There was a modest difference in pharmacokinetic profile between male and female subjects. None of the subjects experienced a serious adverse event (SAE) or an AE of moderate or severe intensity. The investigator reported that 17 of the 28 subjects had mild treatment-emergent AEs that resolved without any concomitant treatment or intervention. No clinically significant changes in vital signs or ECG parameters were observed.

Conclusions This study revealed the pharmacokinetic characteristics and good safety profile of dabigatran in healthy Chinese subjects.

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1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Thromboembolic complications, particularly stroke and systemic embolism, are a major cause of morbidity and mortality in patients with AF [1–3]. In recent years, the therapy most commonly used for stroke prevention in patients with AF has been vitamin K antagonists (VKAs, e.g. warfarin). However, warfarin has a high risk of serious haemorrhagic complications (especially in the elderly), so it requires frequent monitoring, and its efficacy is dependent on nutritional status [4, 5]. Efforts have been made to identify non-vitamin K antagonist oral anticoagulants (NOACs). Currently available NOACs include the direct factor Xa inhibitors apixaban, edoxaban and rivaroxaban, as well as the direct thrombin (factor IIa) inhibitor dabigatran [6].

Dabigatran is a potent, competitive, reversible direct thrombin inhibitor. The amidine group of dabigatran forms a salt bridge with the carboxylate of the aspartate residue Asp189. Hydrophobic interactions occur between the piperidine ring and the moiety with the proximal and distal pockets of the active site of thrombin [7]. Dabigatran blocks thrombus formation by directly inhibiting the thrombin-dependent conversion of fibrinogen to fibrin. However, due to its high polarity, dabigatran is not bioavailable orally. As shown in Fig. 1, to improve its bioavailability and potency in vivo, a prodrug of dabigatran—dabigatran etexilate (Pradaxa, BIBR 1048, Boehringer Ingelheim)—was developed by introducing an ethyl group at the carboxylic acid group and a hexyloxycarbonyl side chain at the amidine group [7–9]. After oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalyzed hydrolysis [10].

Dabigatran etexilate was first authorized for use in all member states of the European Economic Area (EEA) via a centralized procedure on 18 March 2008. As of 15 June 2018, dabigatran had been authorized in 109 countries worldwide. In China, dabigatran etexilate was first approved for the prevention of stroke and systemic embolism in adults with nonvalvular atrial fibrillation (NVAF) and one or more risk factors on 22 February 2013.
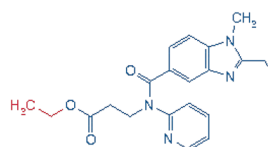
Pharmacokinetic data in Japanese and Caucasians are available from several pharmacokinetic studies. These data show that the pharmacokinetics and pharmacodynamics of dabigatran are comparable in Japanese and Caucasian subjects [11]. Since pharmacokinetic data on dabigatran in Chinese subjects are limited, the study reported here aimed
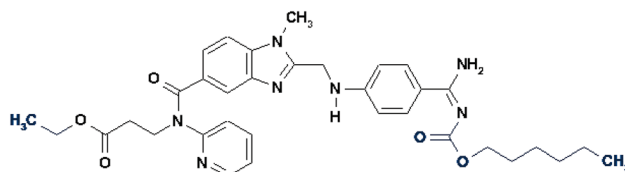
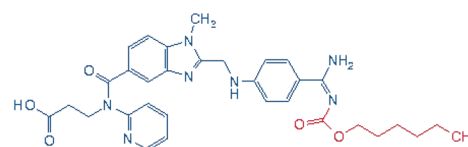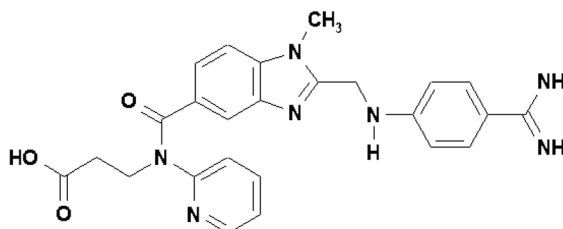**Fig. 1** The dabigatran etexilate prodrug concept

to provide further information in this regard. Thus, in the present study, the pharmacokinetics and safety profile of dabigatran in healthy Chinese subjects were evaluated for the two doses—110 mg twice daily (bid) and 150 mg bid—adopted for the registration of dabigatran etexilate.

2 Subjects and Methods

This trial was conducted between October 2009 and November 2009 at Peking University Third Hospital Drug Clinical Trial Centre.

2.1 Study Subjects

A total of 28 healthy volunteers (14 male and 14 female) aged 18–45 years with a body mass index (BMI) of 18–25 kg/m^2 were included. The inclusion and exclusion criteria are shown in Table S1 of the Electronic supplementary material (ESM). Subjects were screened within 14 days before drug administration. The screening process considered demographics, height and weight, inclusion/exclusion criteria, relevant medical history and concomitant medication. Following screening, subjects who were eligible to participate in the trial and wished to do so were required to given their written informed consent. A flow chart for screening and subject recruitment is shown in Table S2 of the ESM. The studies were conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) as well as local guidelines. The study protocol and informed consent form were approved by the Ethics Committee for Clinical Trials, Peking University Third Hospital.

2.2 Study Design

This was an open-label, single-centre, phase I study. Dabigatran etexilate was provided by Boehringer Ingelheim Pharma GmbH & Co. KG (Biberach, Germany). Eligible subjects were randomized in a balanced fashion into two groups corresponding to the two dosages tested (110 and 150 mg). Subjects received a single dose (either 110 or 150 mg) of dabigatran on day 1, then a two-day break, and then two doses (either 110 or 150 mg) per day on days 4–9 followed by a final dose in the morning of day 10. Dabigatran etexilate was administered to patients in a fed condition in this study. During days 4–9, subjects took the study medication (110/150 mg) with a glass of water (150 mL) immediately after (within 30 min of) breakfast and dinner at the same time in the morning and the evening (8:00–8:30 am/pm) to ensure a dose interval of 12 h. The medication was administered in the sitting position under the supervision of the investigator or subinvestigator.

2.3 Blood Sample Collection and Storage

Venous blood samples were collected 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 h after the administration of the single dose on day 1. Venous blood samples were also collected before drug administration in the morning on days 4, 5, 6, 7, 8 and 9, as well as before drug administration in the evening on days 8 and 9. In addition, venous blood samples were collected just before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 72 h after the final administration of the drug in the morning of day 10.

To quantify analyte plasma concentrations, 4 mL of blood were collected in an EDTA tube and centrifuged immediately at about 3000× g for 10 min at 4 °C. The resulting plasma was divided into two aliquots of about 1 mL and placed in appropriately labelled polypropylene tubes before being immediately frozen at −70 °C.

2.4 Pharmacokinetic Assessment

2.4.1 Quantitative Determination of Dabigatran

Dabigatran is known to conjugate with glucuronic acid, yielding pharmacologically active acyl glucuronides. Unconjugated dabigatran and total (unconjugated + glucuronide-conjugated) dabigatran were determined in the plasma samples using a fully validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) method.

The internal standard used was [^{13}C$_6$]-labelled dabigatran. The linear calibration curves covered the range 1–400 ng/mL in undiluted plasma samples. To determine unconjugated dabigatran, a 50.0-µL aliquot of plasma was diluted with 50 µL of 0.2 M ammonium formate buffer (pH 3.5), spiked with 40 µL of internal standard spiking solution (an aqueous solution of 100 ng/mL [^{13}C$_6$] dabigatran), and mixed well. The samples were then centrifuged for three minutes at 4 °C. To determine total dabigatran, a 50.0-µL aliquot of plasma was spiked with 40 µL of internal standard spiking solution (an aqueous solution of 100 ng/mL [^{13}C$_6$] dabigatran) and mixed with 20.0 µL of 0.2 M NaOH. After 2 h of incubation at 37 °C, the samples were acidified with 30 µL of 0.2 M HCl, mixed, and then centrifuged for 3 min at 4 °C.

For each determination, an aliquot of the resulting supernatant was transferred to an autosampler vial. The analytes were extracted by column switching (on-line solid-phase extraction) on Grom Oasis HLB material (60 × 1 mm; 60 µm particle size) and were chromatographed on an analytical C18 reversed-phase high-performance liquid chromatography (HPLC) column (Merck Purospher Star RP 18; 55 × 2 mm, 3 µm particle size) with gradient elution. Transitions from $m/z = 472$ to $m/z = 289$ and from $m/z = 478$ to $m/z = 295$ were recorded for dabigatran and [^{13}C$_6$] dabigatran, respectively.

Assay performance data demonstrated that the selectivity, accuracy and precision of the method were adequate: quality controls showed a mean deviation from their target concentration (accuracy) of $\leq 3.29\%$ and a mean coefficient of variation (precision) of $\leq 3.82\%$.

2.4.2 Pharmacokinetic Parameters

The following pharmacokinetic parameters were determined for unconjugated and total dabigatran after the initial single dose on day 1: maximum measured concentration (C_{max}), time from dose to the maximum measured concentration (t_{max}), area under the concentration–time curve ($AUC_{\tau,1}$), $AUC_{0-\infty}$, elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume (V_z/F). The following pharmacokinetic parameters were determined after the final dose (i.e. at steady state at the end of the multiple-dose period) on day 10: $C_{max,ss}$, $t_{max,ss}$, $AUC_{\tau,ss}$, and $t_{1/2,ss}$. The accumulation ratios $R_{A,AUC}$ and $R_{A,Cmax}$ (corresponding to $AUC_{\tau,ss}$/$AUC_{\tau,1}$ and $C_{max,ss}$/C_{max}, respectively) were calculated. Dose proportionality was assessed in a qualitative manner.

2.5 Safety Assessment

All adverse events (AEs) that occurred during the course of the study were recorded and coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA, version 12.0). The frequency of subjects with AEs was calculated, and the severity of each AE and its relationship to the study drug were recorded. Analyses of adverse events were qualitative in nature. All analyses of AEs were based on the number of subjects with AEs, not the number of AEs. To facilitate analysis, AE data were combined into AE records in a two-step procedure. In the first step, AE occurrences (i.e. AE entries on the CRF) were converted into AE episodes. In the second step, AE episodes were condensed into AE records provided that the episodes were reported with the same term at the respective MedDRA level and that the episodes were assigned to the same treatment.

Routine clinical laboratory tests, physical examinations, and vital sign and 12-lead electrocardiogram (ECG) measurements were performed throughout the trials. Descriptive statistics were provided by dose group for the clinical laboratory tests, vital signs, and ECG measurements.

2.6 Statistical Analysis

The sample size was 14 subjects per group. The planned sample size was not based on a power calculation. Fourteen subjects per group was considered to be sufficient for the exploratory evaluation of safety and pharmacokinetics in the present single/multiple-dose study in China.

All analyses were performed using SAS® version 9.1.3. Descriptive statistics were calculated for concentrations and all pharmacokinetic parameters of unconjugated dabigatran and total dabigatran. For the comparison of morning versus evening unconjugated and total trough dabigatran concentrations, a fixed effect term was added to the linear mixed model on a logarithmic scale to identify morning and evening doses. Two-sided 95% CIs (confidence intervals) for the expected difference in mean least square of the log-transformed concentration between morning and evening were calculated and back-transformed by exponentiation. The significance level α was set to 0.05. No adjustment of α was performed since this analysis was considered to be explorative.

3 Results

3.1 Subjects

A total of 28 healthy subjects (14 males and 14 females) were randomized to the two treatment groups (110 or 150 mg) in a 1:1 ratio. One subject in the 150 mg bid group withdrew from the study due to AEs. All 28 subjects were analyzed for pharmacokinetics and safety.

As shown in Table 1, the mean age, height, weight and BMI were 27.8 (standard deviation [SD]: $\pm$ 5.4; range: 18.8–42.9) years, 166 (SD: $\pm$ 7.0; range: 153–179) cm, 60.5 (SD: $\pm$ 6.1; range: 49.5–74.5) kg and 22.0 (SD: $\pm$ 1.5; range: 18.9–24.4) kg/m^2, respectively. No subjects received concomitant therapy during this study. Twelve subjects reported at least one relevant item in their medical history, but there were no active medical conditions at baseline.

3.2 Pharmacokinetics

The median times taken for the plasma concentration of total dabigatran to reach its peak in healthy Chinese subjects after the first and last doses under fed conditions (i.e. t_{max} and $t_{max,ss}$, respectively) were 3–4 h, and the plasma concentration declined following the first and last doses with elimination half-lives ($t_{1/2}$ and $t_{1/2,ss}$, respectively) of 10.7–10.9 h (Fig. 2). The shape of the plasma concentration profile of unconjugated dabigatran was similar to that of total dabigatran (data not shown). Since glucuronic acid conjugates of dabigatran have similar pharmacodynamic activities to the active dabigatran moiety itself, total dabigatran was considered the primary biorelevant parameter for the pharmacokinetics of dabigatran, so only total dabigatran is reported hereafter.

For the patients who received the 110 mg bid dose, the geometric mean values of $C_{max,ss}$ and $AUC_{\tau,ss}$ in plasma were 133 ng/mL and 805 ng h/mL, respectively, and the

Table 1 Demographic data of study subjects

Characteristic	Dabigatran etexilate 110 mg (N=14)	Dabigatran etexilate 150 mg (N=14)	Total (N=28)
Age (years)			
Mean (SD)	29.3 (5.6)	26.2 (4.9)	27.8 (5.4)
Median (range)	28.1 (23.0–42.9)	26.1 (18.8–36.7)	27.7 (18.8–42.9)
Sex, n (%)			
Male	7 (50%)	7 (50%)	14 (50%)
Female	7 (50%)	7 (50%)	14 (50%)
Race, n (%)			
Asian	14 (100.0)	14 (100.0)	28 (100.0)
Height (cm)			
Mean (SD)	165 (7.0)	166 (7.4)	166 (7.0)
Median (range)	166.5 (153–176)	166.0 (153–179)	166.5 (153–179)
Weight (kg)			
Mean (SD)	59.8 (4.6)	61.2 (7.5)	60.5 (6.1)
Median (range)	59.8 (53.5–70.0)	60.8 (49.5–74.5)	60.0 (49.5–74.5)
BMI (kg/m^2)			
Mean (SD)	21.9 (1.3)	22.2 (1.7)	22.0 (1.5)
Median (range)	21.5 (20.4–24.4)	22.6 (18.9–24.3)	22.1 (18.9–24.4)

SD standard deviation, *BMI* body mass index

corresponding values for patients who received the 150 mg bid dose were 195 ng/mL and 1250 ng·h/mL, respectively (Table 2). The increase in exposure with dose did not show any apparent deviation from dose proportionality. The accumulation ratios $C_{max,ss}/C_{max}$ (= $R_{A,Cmax,13}$) and $AUC_{\tau,ss}/AUC_{\tau,1}$ (= $R_{A,AUC,13}$) were approximately 1.51 in and 1.70, respectively.

As shown in Table 3, female subjects experienced slightly higher exposure than male subjects. Female exposure after the initial single dose (i.e. $AUC_{0-\infty}$ and C_{max}) was 1.4–7.7% higher than male exposure, while female exposure in the steady state at the end of the multiple-dose period (i.e. $AUC_{\tau,ss}$ and $C_{max,ss}$) was 9.1–19.8% higher than male exposure.

The difference between the least square mean trough total dabigatran concentrations measured in the morning and the evening (and the 95% CI) is shown for each dosage group in Table 4. The trough concentrations measured before the evening doses were lower than those measured before the morning doses in both the 110 mg bid group and the 150 mg bid group. Since the CI for each group included values above and below 1.00, the difference in concentration between morning and evening was not statistically significant for either group.

3.3 Safety

No serious adverse events (SAE) or AEs of a moderate or severe intensity were reported during the study. One subject in the 150 mg bid group withdrew prematurely due to AEs (the subject experienced increases in C-reactive protein and alanine aminotransferase as well as haematuria, epistaxis and haemorrhoidal haemorrhage); however, those AEs resolved fully within four days after study drug discontinuation.

The investigator reported that 17 subjects had treatment-emergent AEs: 12 of the 14 subjects (85.7%) in the dabigatran etexilate 150 mg bid group and 5 of the 14 subjects (35.7%) in the dabigatran etexilate 110 mg bid group. Among the 17 subjects with reported AEs, 15 had AEs that were considered to be drug-related by the investigator. However, only 14 AEs among 9 subjects were associated with clinical signs or symptoms during this trial. All of the reported AEs were mild in intensity and resolved without any concomitant treatment or intervention. The most frequently reported type of AE with clinical signs or symptoms was headache, which was reported by three subjects. Two of the 14 subjects (14.3%) in the dabigatran etexilate 110 mg bid group and 6 of the 14 subjects (42.9%) in the dabigatran etexilate 150 mg bid group had an AE associated with overt, observable and/or laboratory-detectable bleeding (Table 5). All cases of bleeding, whether overt or only detected by urinalysis or occult faecal blood testing, were mild and resolved without therapy.

There were no clinically significant changes in vital signs or ECG parameters.

Fig. 2 Arithmetic mean (± SD) plasma concentration–time profiles of total dabigatran after the initial single dose (**a**) and after the final dose (i.e. at the end of the multiple-dose period; **b**) of 110 mg and 150 mg dabigatran etexilate. The starting point on X axis in (**b**) is the time of the morning dose on Day 4
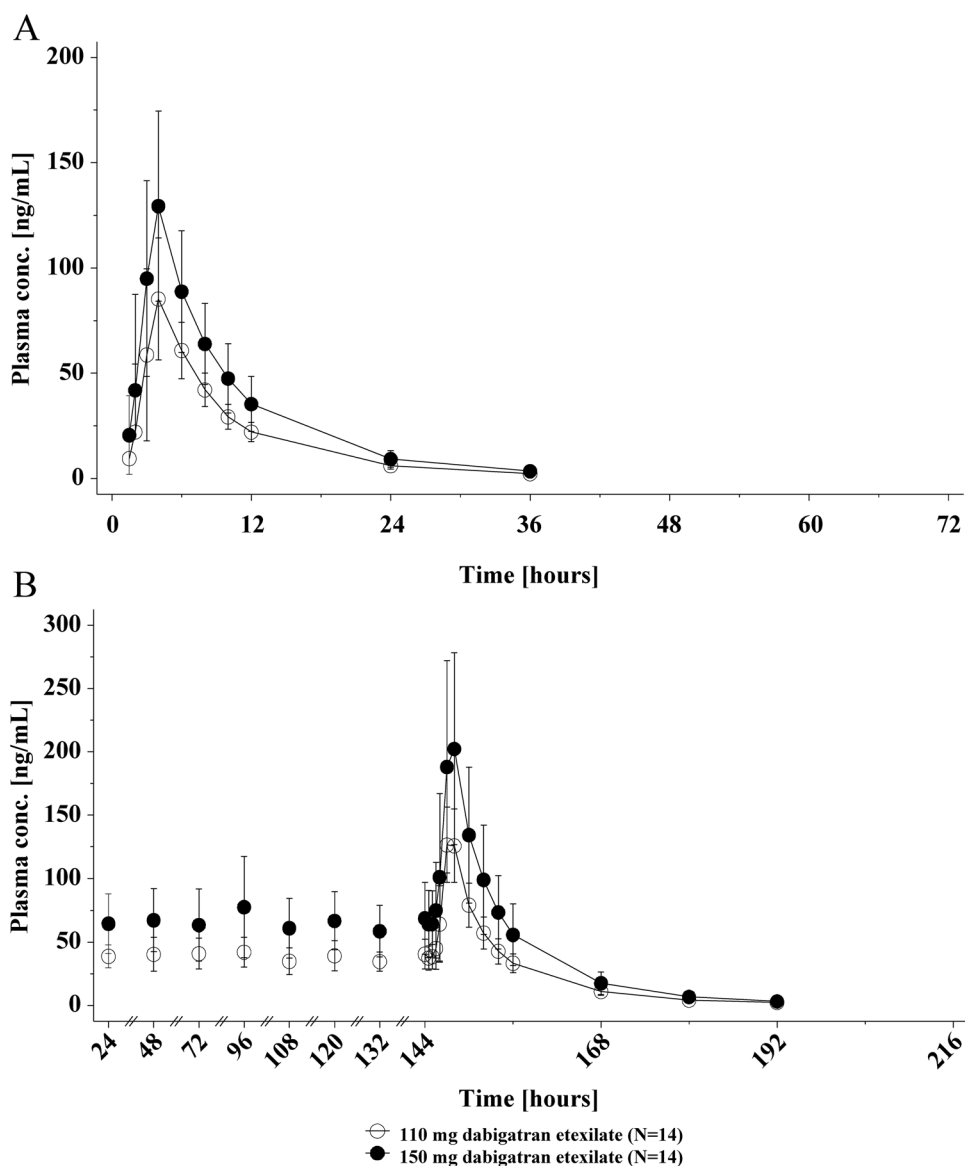
4 Discussion

Pharmacokinetic data in Japanese and Caucasian subjects are available from several pharmacokinetic studies [11]. To supplement the information available on the pharmacokinetic profile of dabigatran in Chinese subjects, the present study investigated the pharmacokinetics and safety of dabigatran following oral administration of single and multiple oral doses of 110 and 150 mg bid (the registered doses of dabigatran etexilate) to Chinese patients.

Consistent with previous observations in Japanese and Caucasian subjects [12, 13], the plasma concentration of total dabigatran reached its peak after median times t_{max} (after the single dose) and $t_{max,ss}$ (at the end of the multiple-dose period) of 3–4 h under fed conditions, and declined with elimination half-lives $t_{1/2}$ (after the single dose) and

$t_{1/2,ss}$ (at the end of the multiple-dose period) of 10.7–10.9 h in healthy Chinese subjects. Exposure in healthy Chinese subjects was comparable with that observed in healthy Japanese subjects and slightly higher than that seen in Caucasian subjects [11]. A modest gender difference in exposure was observed in Chinese subjects: females experienced slightly higher exposure than male subjects, which was also observed in Caucasian subjects. Such modest differences are explained by gender-dependent renal clearance [13].

The pharmacokinetic aspects observed in this trial indicate that the pharmacokinetic profile of dabigatran in Chinese subjects is not significantly different from the corresponding profiles in Japanese and Caucasian subjects. Indeed, the registered dosing regimen of dabigatran in China is the same as that registered with the European Medicines Agency (EMA).

Table 2 Pharmacokinetic parameters of total dabigatran following the administration of the initial (single) dose and the final dose of 110 mg and 150 mg dabigatran etexilate

Parameter	Dabigatran etexilate 110 mg			Dabigatran etexilate 150 mg		
	N	gMean	gCV (%)	N	gMean	gCV (%)
C_{max} (ng/mL)	14	87.6	30.8	14	132.0	29.8
t_{max} (h) [a]	14	4.00	(3.00–8.00)	14	4.00	(3.00–10.0)
$AUC_{\tau,1}$ (ng·h/mL)	14	474	26.5	14	731	27.6
$AUC_{0-\infty}$ (ng·h/mL)	14	697	23.9	14	1070	27.5
$t_{1/2}$ (h)	14	8.45	27.2	14	8.02	19.4
CL/F (mL/min)	14	1970	23.9	14	1760	27.5
V_z/F (L)	14	1450	27.6	14	1220	27.8
$C_{max,ss}$ (ng/mL)	14	133	23.0	13	195	39.0
$t_{max,ss}$ (h) [a]	14	3.00	(3.00–4.00)	13	4.00	(3.00–4.00)
$AUC_{\tau,ss}$ (ng·h/mL)	14	805	19.9	13	1250	40.6
$t_{1/2,ss}$ (h)	14	10.9	24.7	13	10.7	20.7
$R_{A,AUC,13}$	14	1.70	19.1	13	1.71	37.5
$R_{A,Cmax,13}$	14	1.51	26.0	13	1.47	43.5

gCV geometric coefficient of variation, *gMean* geometric mean, C_{max} maximum measured concentration in plasma after the first dose, $C_{max,ss}$ maximum measured concentration in plasma after the final dose (on day 10) of the multiple dose period, t_{max} time from initial (single) dose to maximum measured concentration, $t_{1/2}$ terminal half-life, *CL* clearance, *V* apparent volume of distribution, R_A accumulation ratio, $AUC_{\tau,1}$ area under the curve over a uniform dosing interval τ after administration of the first dose on day 1, $AUC_{\tau,ss}$ area under the curve over a uniform dosing interval τ at steady state, $AUC_{0-\infty}$ area under the curve over the time interval from 0 extrapolated to infinity, $t_{max,ss}$ time from last dose to the maximum concentration at steady state over a uniform dosing interval τ, $t_{1/2,ss}$ terminal half-life at steady state, $R_{A,AUC,13}$ accumulation ratio after administration of the final dose (on day 10) of the multiple dose period τ (i.e. the ratio of $AUC_{\tau,ss}$ to $AUC_{\tau,1}$), $R_{A,Cmax,13}$ accumulation ratio after administration of the final dose (on day 10) of the multiple dose period τ (i.e. the ratio of $C_{max,ss}$ to C_{max})

[a] median (range)

Table 3 Pharmacokinetic parameters of total dabigatran by gender

Parameter	Male			Female		
	N	gMean	gCV (%)	N	gMean	gCV (%)
110 mg dabigatran etexilate						
C_{max} (ng/mL)	7	87.0	20.5	7	88.2	40.9
$AUC_{\tau,1}$ (ng·h/mL)	7	457	20.3	7	492	33.1
$AUC_{0-\infty}$ (ng·h/mL)	7	678	21.1	7	718	27.9
$C_{max,ss}$ (ng/mL)	7	121	25.0	7	145	18.1
$AUC_{\tau,ss}$ (ng·h/mL)	7	739	18.6	7	877	18.3
150 mg dabigatran etexilate						
C_{max} (ng/mL)	7	129	31.2	7	135	30.7
$AUC_{\tau,1}$ (ng·h/mL)	7	712	31.8	7	750	25.0
$AUC_{0-\infty}$ (ng·h/mL)	7	1040	36.4	7	1090	18.3
$C_{max,ss}$ (ng/mL)	7	187	32.4	6	204	49.0
$AUC_{\tau,ss}$ (ng·h/mL)	7	1190	36.3	6	1340	48.3

gCV geometric coefficient of variation, *gMean* geometric mean, C_{max} maximum measured concentration in plasma, $C_{max,ss}$ maximum measured concentration in plasma after the final dose (on day 10) of the multiple dose period, $AUC_{\tau,1}$ area under the curve over a uniform dosing interval τ after administration of the first dose on day 1, $AUC_{\tau,ss}$ area under the curve over a uniform dosing interval τ at steady state, $AUC_{0-\infty}$ area under the curve over the time interval from 0 extrapolated to infinity

The trough concentrations before the evening dose were not statistically significantly different from the trough concentrations before the morning dose in both the 110 mg bid group and the 150 mg bid group, suggesting that there was no obvious effect of circadian rhythm on the pharmacokinetics of dabigatran.

In the phase III RE-LY study, dabigatran etexilate dosages of 110 and 150 mg bid were well tolerated, and there

Table 4 Comparison of morning and evening trough total dabigatran concentrations (ng/mL) in the 110 mg bid group and the 150 mg bid group

	Morning	Evening	Difference (morning – evening)		
	LS mean	LS mean	LS mean	95% CI	*p* value
110 mg (*N* = 14)	38.9135	33.3648	1.1663	(0.9660, 1.4081)	0.105
150 mg (*N* = 13)	64.8439	54.7861	1.1836	(0.8701, 1.6099)	0.269

LS mean least square mean, *CI* confidence interval

Table 5 Patients who had AEs involving bleeding or lab tests for haemoglobin

	Dabigatran etexilate 110 mg (*N* = 14)		Dabigatran etexilate 150 mg (*N* = 14)	
	N	%	N	%
Number of subjects with any AEs involving bleeding or lab tests for haemoglobin	2	14.3	6	42.9
AEs by preferred term				
Occult blood positive	1	7.1	3	21.4
Haematuria	1	7.1	3	21.4
Haemorrhoidal haemorrhage	0	0.0	2	14.3
Epistaxis	0	0.0	1	7.1

AE adverse event

was no apparent difference between Chinese and Caucasian patients in safety concern parameters or blood coagulation parameters after the administration of multiple doses [14]. Both dosages of dabigatran showed good tolerability in the current study. No SAEs, deaths or AEs of a moderate or severe intensity were reported during this study. All reported AEs were mild in intensity and resolved without any concomitant treatment.

5 Conclusion

This study demonstrates that dabigatran displays similar pharmacokinetic characteristics in healthy Chinese subjects to those seen in Japanese and Caucasian subjects in previous studies, together with a good safety profile.

Dr Dietmar Gansser and Ningning Dong are employees of Boehringer Ingelheim.

Compliance with Ethical Standards

Conflict of Interest NY and AH are employees of Nippon Boehringer Ingelheim Co., Ltd.. DJ was the principal investigator of this trial. Both YL and LH participated in the clinical study. The authors report no other conflicts of interest in this work.

Ethical Approval The study was approved by the Ethics Committee for Clinical Trials, Peking University Third Hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, and in accordance with the principles of Good Clinical Practice and local guidelines.

Informed Consent Written informed consent was obtained from all individual participants prior to study enrolment.

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