A Phase I, single and continuous administration study of Safety, tolerability and pharmacokinetics of neorudin, a noval recombinant anticoagulant protein, in healthy subjects

Yu-bin Liu[1], Mei-xia Wang[2], Xiao-na Dong[1], Jia He[3], Lin Zhang[1], Ying Zhou[1], Xia Xia[3], Gui-fang Dou[1], Chu-tse Wu[1], and Ji-de Jin[1]

[1]Beijing Institute of Radiation Medicine
[2]Beijing You'an Hospital, Capital Medical University
[3]Beijing SH Biotechnology Co., Ltd.

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Abstract

AIMS: The aims of the study were to evaluate the tolerability, safety and pharmacokinetics of single and continuous administration of recombinant neorudin (EPR-hirudin, EH) by intravenous injection in healthy subjects, and to provide a safe dosage range for phase II clinical research. METHODS: A single and continuous administration dose phase I clinical study was conducted. Forty-four subjects were received EH as single-dose of 0.2-2.0 mg/kg by intravenous bolus plus drip; Eighteen healthy subjects were randomly divided into 3 dose groups (0.15-0.45 mg/kg/h) with 6 cases in each group in the continuous administration trial. RESULTS: Single or continuous doses of neorudin were generally well tolerated in healthy adult subjects. There were no serious adverse events (SAEs), and all adverse events (AEs) were mild to moderate. No subjects withdrew from the trial due to adverse events. There were no clinically relevant changes in physical examination, clinical chemistry, urinalysis or vital signs. The incidence of adverse events was not significantly related to the dose and systemic exposure. After the single-dose and continuous administration, the serum EH concentration reached a peak at 0.083h,the exposure increased with the increase of the administered dose with the mean half-life (T1/2) ranging from 1.7 to 2.5h, the clearance (Cl) ranging from 123.9 to179.7 mL/h/kg, and the apparent volume of distribution (Vd) ranging from 402.7 to 615.2 mL/kg. CONCLUSIONS: The safety, tolerability and pharmacokinetics characteristics of EH can be used to guide rational drug dosing and choose therapeutic regimens in subsequent clinical studies.

A Phase I, single and continuous administration study of Safety, tolerability and pharmacokinetics of neorudin, a noval recombinant anticoagulant protein, in healthysubjects

Liu Yu-Bin1 Wang Mei-Xia2 Dong Xiao-Na1 He-Jia3 Zhang Lin1 Zhou Ying1 Xia-Xia3 Dou Gui-Fang1 Wu Chu-tse1* Jin Ji-De1*

1 Beijing Institute of Radiation Medicine,Beijing 100850,China

2 Beijing You'an Hospital, Capital Medical University, Beijing 100069,China

3 Beijing SH Biotechnology Co., Ltd., Beijing 100093,China

* Corresponding author,Wu Chu-tse E–mail:*wuct@bmi.ac.cn* ; Jin Ji-De E–mail:*jinjide505@163. com*

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subjects, and to provide a safe dosage range for phase II clinical research.

METHODS: A single and continuous administration dose phase I clinical study was conducted. Forty-four subjects were received EH as single-dose of 0.2-2.0 mg/kg by intravenous bolus plus drip; Eighteen healthy subjects were randomly divided into 3 dose groups (0.15-0.45 mg/kg/h) with 6 cases in each group in the continuous administration trial.

RESULTS: Single or continuous doses of neorudin were generally well tolerated in healthy adult subjects. There were no serious adverse events (SAEs), and all adverse events (AEs) were mild to moderate. No subjects withdrew from the trial due to adverse events. There were no clinically relevant changes in physical examination, clinical chemistry, urinalysis or vital signs. The incidence of adverse events was not significantly related to the dose and systemic exposure. After the single-dose and continuous administration, the serum EH concentration reached a peak at 0.083h,the exposure increased with the increase of the administered dose with the mean half-life ($T_{1/2}$) ranging from 1.7 to 2.5h, the clearance (Cl) ranging from 123.9 to179.7 mL/h/kg, and the apparent volume of distribution (Vd) ranging from 402.7 to 615.2 mL/kg.

CONCLUSIONS : The safety, tolerability and pharmacokinetics characteristics of EH can be used to guide rational drug dosing and choose therapeutic regimens in subsequent clinical studies.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

Animal studies have suggested that neorudin has a significant anticoagulant activity and low bleeding feature, as well as detectible pharmacokinetic properties.

WHAT THIS STUDY ADDS?

This first study in humans provided some further important reference information about the tolerability, safety and pharmacokinetics of EH in healthy subjects for next clinical investigation.

1 Introduction

With growing populations and longer life expectancy, we will see an increase in the prevalence of thrombus formation.[1] Thrombotic events can be potentially life threatening and may prolong the length of hospital stay and result in chronic disability[2]. Thrombosis is the most common underlying pathology of the three major cardiovascular disorders: ischemic heart disease (acute coronary syndrome, ACS), stroke, and venous thromboembolism (VTE).[3] ACS, the acute manifestation of ischemic heart disease, resulting from coronary arterial thrombus formation, remains a major cause of morbidity and mortality worldwide.[4]VTE, primarily including pulmonary embolism and deep venous thrombosis, affects an estimated 750,000 people in the United States each year and causes more than 100,000 deaths annually. 15.4% of people with thromboembolism died within 90 days after the index diagnosis.[5,6]

Low-molecular heparin and low-dose unfractionated heparin can prevent deep vein thrombosis of the lower extremities.[7,8]Unlike heparin, hirudin is an antithrombotic substance produced by the salivary glands of the medicinal leech Hirudo medicinalis which can directly act on thrombin and effectively inhibit both free and bound thrombin. In some animal models of deep vein injury, hirudin is a more effective antithrombotic drug than heparin.[9,10]However, treatment with hirudin increases the risk of systemic bleeding, which is its main adverse effect.[11,12]

Neorudin (EPR-hirudin, EH) is a targeted hirudin variant 2-Lys47(HV2) fusion protein, which is composed of 68 amino acids, with a theoretical molecular weight of 7284 Da.[13-15] EH was developed as a prodrug of HV2 by introducing EPR (Glu-Pro-Arg), which is recognized and cleaved by FXIa, into the N-terminal of HV2.[16] EH exerts antithrombotic effects by releasing its active metabolite, HV2, at the thrombus site via FXIa-mediated cleavage of EPR, resulting in direct inhibition of thrombin. However, when intact, EH does not display anticoagulant activity. The construction and mechanism of EH determined that it not only effectively inhibited thrombus formation but also reduced the risk of bleeding by increasing the specificity and efficiency of hirudin.[17,18]

Pre-clinical studies[19] have shown that EH was effective and safe in the treatment of thrombosis in rat models of thrombus formation. Compared with low-molecular-weight heparin and hirudin, the bleeding side effects of EH were lower when the antithrombotic effects were similar. After rhesus monkeys were given EH 1.0, 3.0 and 6.0 mg/kg by intravenous bolus and drip, the half-life($T_{1/2}$) of EH were 1.2±0.6, 1.3±0.3 and 1.0±0.1h, and Tmax was 0.05±0.00 h. The clinical indication to be used of EH was the prevention and treatment of arteriovenous thrombosis.

The purpose of this first-in-human study was to assess the elementary safety and pharmacokinetics of EH in healthy volunteers, and this study was registered at chinadrugtrials.org.cn (Clinical Trial Registry number: CTR20160444) [PRC CFDA. China drug trials. http://www.chinadrugtrials.org.cn/eap/clinicaltrials.searchlist?keywords=CTR20160444. (Accessed 15 March 2020)].

2 Methods

2.1 Subjects

Healthy, nonsmoking men or women aged 18–45 years with a body mass index of 19–26 kg /m^2 (Weight[?]50kg) were eligible for inclusion in the study. The health status was determined by a prestudy medical history, physical examination and clinical laboratory evaluations. Women who were nursing or pregnant and subjects who were infected with human immunodeficiency virus, hepatitis B, hepatitis C viruses or syphilis were excluded from the study. The subjects were not allowed to consume cigarette, alcohol or grapefruit-containing products to screening and during admission and follow-up. The subjects who have blood donation history or significant blood loss in the past 3 months ([?]400ml) were excluded from the study.

2.2 Design

A Phase I, single and continuous administration study of safety, tolerability and pharmacokinetics of EH by intravenous injection in healthy subjects was conducted. The study, sponsored by Beijing SH Biotechnology Co., Ltd. and Beijing Institute of Radiation Medicine, was performed at the Phase I Unit of Beijing You'an Hospital, Capital Medical University. Both studies were approved by applicable institutional review boards/ethics committees and conducted in accordance with country regulations, the International Conference on Harmonisation Good Clinical Practice guidelines, and the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

2.2.1 Determination of the EH dose escalation range

According to the "Guidelines for Estimating the Maximum Recommended Starting Dose of Drugs for the First Clinical Trial of Healthy Adult Volunteers" promulgated by the CENTER FOR DRUG EVALUATION and the No Observed Adverse Effect Level (NOAEL) calculation results of preclinical animal trials, it was known that the most suitable NOAEL of EH for long-term toxicity testing of cynomolgus monkeys was 1.3 mg/kg. The recommended clinical dose of REFLUDAN,[20]a similar drug from Bayer, approved by the FDA on March 6, 1998, for the treatment of HIT (Heparin-Induced Thrombocytopenia) was 0.4 mg/kg intravenous bolus first, and then 0.15 mg/kg/h of continuous intravenous drip for 2-7 days. Preclinical studies of EH showed that 0.4mg/kg of hirudin was equivalent to 0.416mg/kg EH, and the pharmacodynamic dose range of EH animal test was about 0.06˜2.13mg/kg. The preclinical mouse and cynomolgus acute toxicity test of this drug showed that its Maximum Tolerated Dose (MTD) was much higher than the planned clinical effective dose. It was safe and reasonable to initially consider 0.2˜2.0mg/kg as the dose increase range of this clinical trial.

2.2.2 Single dose regimen

In the single-dose trial, 4 subjects were enrolled in the preliminary trial, and 40 subjects were enrolled in the formal trial. In the preliminary trial, considering that the test drug was first used in humans, in order to protect the safety of the subjects to the utmost extent, at the beginning of the preliminary trial (test

drug 0.2mg/kg), 1 healthy subject was enrolled and observed for 7 days to confirm the safety of EH,then the remaining 3 subjects were re-entered and observed for 7 days. In the formal trial, the randomized, placebo-controlled, dose-escalating study was divided into 5 dose group, 8 cases per group (Test drug: placebo=6:2), and the order of increasing dose was: 0.4, 0.8, 1.2, 1.6, 2.0 mg/kg per administration. The research center determined the drug grouping information of the subjects according to the random system. The single administration process was shown in Figure 1.

2.2.3 Continuous administration

There were 3 dose open groups for continuous administration, with 6 cases in each group, and the time of continuous administration was 24 hours. After the administration, the subjects were discharged after 2 days of hospitalization, and the trial ended after the 28th day. In each dose group, the dose of intravenous bolus (bolus 30 seconds or more) was 0.4 mg/kg, and the increasing range of maintenance dose was 0.15, 0.30 and 0.45 mg/kg/h. One subject in each group was first enrolled, and the remaining subjects were then enrolled after observing that there was no safety problem at least 48 hours after the end of the administration. It was confirmed that there was no safety problem after the last subject in the previous dose group had completed the observation to at least the 7th day, then the subjects were entered for the next dose group. Supervising and guiding the process of drug clinical trials was performed by establishing a data and safety monitoring committee. The continuous administration process was shown in Figure 2.

2.3 Safety assessment

The following clinical safety assessments were included in the study: a physical examination, the vital signs (height, weight, blood pressure, heart rate, axillary temperature and respiratory rate), clinical laboratory tests (full blood count, urine routine, blood chemistry, coagulation function, stool routine & occult blood, 12-lead ECG cardiac monitoring, chest X-ray examination) and recording of the adverse events. Adverse experiences were monitored throughout the study. The investigators evaluated all the clinical adverse events in terms of the intensity (mild, moderate or severe), duration, severity, outcome and relationship to the study drug.

2.4 Pharmacokinetic assessments

2.4.1 Pharmacokinetic study of single dose

Forty-four subjects at 6 dose levels of 0.2-2.0 mg/kg participated in the pharmacokinetic assessment of a single dose. Serum was taken within 5 min before administration, 5min, 15min, 30min after the start of administration, 5 min, 20 min, 40 min, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h after the end of the administration to test the blood drug concentration.

2.4.2 Pharmacokinetic study of continuous administration dose

Eighteen subjects in the 3 dose groups of 0.15, 0.30 and 0.45mg/kg/h participated in the pharmacokinetics analysis of continuous administration dose. Serum was taken within 5 min before administration, 5 min, 30 min, 4h, 8h, 12h and 24h after the start of administration, 5 min, 20 min, 40 min, 1h, 1.5h, 2h, 3h, 4h, 6h, 8h, 12h, 24h after the end of the administration to test the blood drug concentration. In the 0.30 mg/kg/h dose group, plasma was also taken at 5 min, 8 h, 24 h and 5 min after the end of administration to test the blood drug concentration, and urine was collected before administration, 0-4h, 4-8h, 8-12h, 12-16h, 16-20h, 20-24h after administration start, 0-4h, 4-8h, 8-12h, 12-16h, 16-20h, 20-24h, 24-32h, 32-40h, 40-48h after the end of the administration to test the urine drug concentration.

2.5 Data and statistical analysis

The treatment-emergent adverse events (TEAE) and adverse reactions in each dose group were summarized according to the System Organ Class and the Preferred Term. TEAE means an adverse event that occurred at or after the first medication to 28 days (inclusive) after the last medication. The severity of adverse events was classified using NCI CTCAE 4.03.

For safety data such as laboratory, vital signs, electrocardiogram, physical examination, etc., baseline data, post-dose data, and change from baseline were summarized according to each follow-up and each dose group; Regarding whether the test results were normal or not and whether they were clinically meaningful as classified data, a Shift Table was used to describe the change from baseline to each follow-up after administration.

Using the blood/urine PK concentration analysis set, the blood/urine concentration of each planned time point was descriptively summarized, and for each dose group, the concentration-time curve of each subject and the average concentration-time curve of each group was drawn.

The pharmacokinetic data were processed and graphed using computer programs Excel and origin Pro 8.0. The pharmacokinetic parameters were calculated using the non-compartmental model (NCA) of Phoenix 64 (WinNonlin6.3). Medical history and adverse events were coded using MedDRA and past and combined medications were coded using WHO Drug Dictionary.

Statistical analysis was respectively performed for the single-dose and continuous administration by the SAS(r) version 9.4 software (SAS Institute Inc., Cary, NC, USA) and a P-value of 0.05 was considered statistically significant.

3 RESULTS

3.1 Subject characteristics

In single-dose trial, 44 subjects met the selection criteria were received medication to obtain safety data and were included in the safety analysis set. In the continuous administration trial, 18 subjects met the selection criteria were received medication to obtain safety data and were included in the safety analysis set. Summary demographic information about the 62 subjects who completed the study was summarized in Table1. Healthy, non-smoking men or women average aged 27.4–30.9 years with a body mass index of 21.4–23.81 kg/m^2 were eligible for inclusion in the single-dose trial. Healthy, non-smoking men or women average aged 29.7˜30.5 years with a body mass index of 22.65-23.30 kg/m^2 were eligible for inclusion in the continuous administration dose.

3.2 Safety Results

The adverse events (AEs) recorded during the entire study were mild to moderate and well controlled, and most were recovered without treatment. The incidence of adverse events had no statistically difference (P = 0.62) between the test (20 of 34 subjects) and placebo groups (5 of 10 subjects) in the single-dose study. In total, 51 AEs were reported from 20 of the 34 subjects in test group and fourteen of these were considered to be related to the EH by the investigator (Table 2). The incidence of AEs was notably higher in the continuous administration dose study than in the single-dose study. 68 AEs were reported from 17 of the 18 subjects in the continuous administration dose study, and 58 out of the 68 reported AEs were considered by the investigator to be related to EH (Table 3). Hypohemoglobinemia was the main AEs recorded in the single-dose study, while the increase of D-dimer, reticulocyte and activated partial thromboplastin time (APTT) were the main AEs reported in the continuous administration study. However, no treatment or dose-related trend in the incidence of AEs was observed. There were no serious adverse events (SAEs) reported, no subjects were withdrawn due to AEs, and there were no AEs leading to death.

3.3 Pharmacokinetics

The serum or urine samples from 62 subjects participated in the single-dose or the continuous administration dose study were collected for pharmacokinetics analysis using ultraperformance liquid chromatography/tandem mass spectrometry method.[21,22] However, the data from the ten subjects participated in the placebo group were not detected and then were ignored.

3.3.1 Pharmacokinetics after single-dose trial

The mean serum concentration–time data and PK parameters of EH were shown in Table 4 and Figure 3.

Following 0.083h infusion, the serum concentration of EH reached a peak at the end of infusion, and the exposure increased with the increase of the dose. The half-life($T_{1/2}$) of each dose group changed in the range of 1.7˜2.5 h. The Clearance (Cl) of each dose group changed in the range of 123.9˜179.7 mL/h/kg. The apparent volume of distribution (Vd) changed in the range of 402.7˜615.2mL/kg.

The mean serum concentration of EH gradually increased with increasing dose, and the characteristics of serum concentration-time data in each dose group were similar. With the increase of the administered dose, the exposure of hirudin, the active metabolite of EH, in the serum also gradually increased. The trend of EH plasma concentration was similar to hirudin, basically showing a linear law. After 7h of EH administration, the serum hirudin concentration of each dose group was too low to be detected. The ratio of the area under curve of the hirudin to the EH was about 2.4-6.3%(Table 5).

3.3.2 Pharmacokinetics after continuous administration trial

The mean serum concentration–time data and PK parameters of EH were summarized shown in Table 4 and Figure 4. The mean serum concentration gradually increased with increasing dose, and the characteristics of serum concentration–time data in each dose group were similar. With the increase of the administered dose, the exposure of hirudin in the serum gradually increased and the trend of EH plasma concentration was similar to hirudin, basically showing a linear relationship. The hirudin in each dose group was below the lower limit of quantification after 28h of continuous administration, and the EH in each dose group was below the lower limit of quantification after 36h of continuous administration. The 0.45 mg/kg/h group had no significant accumulation after continuous administration, and the accumulation ratio AR_Cmax was less than 1.25. At the doses of 0.15mg/kg/h and 0.30mg/kg/h, the cumulative excretion rates of EH in urine from the start of administration to 48h after the end of administration were 4.6% and 9.9% respectively and the cumulative excretion rates of hirudin were 0.6% and 1.2%(Table 6). The total cumulative excretion rates of EH plus hirudin were 5.2% and 11.0% respectively, suggesting some other metabolites were produced from EH.

4 Discussion

4.1 Safety

This trial was a first-in-human trial conducted in healthy volunteers to explore the safety, tolerability, and pharmacokinetics of EH. The action mechanism and structure determine that neorudin gestates the high safe and low bleeding charaterestics which have already been proved in preclinical studies. In this study, the safety and tolerance of EH was also reconfirmed in healthy subjects within a single-dose of 0.2-2 mg/kg and a continuous 24-hour administration of 0.15-0.45 mg/kg/h. Although the level of hirudin in vivo increased with the increase of EH dose, the level of hirudin was still very low, and almost no bleeding events occurred. The adverse events were mostly reported in the clinical study or application of hirudin, including the adverse reactions related to bleeding and abnormal coagulation tests, such as hypohemoglobin and reticulocyte count increase,[23-25] and were soon recovered after symptomatic treatment or without treatment. The antithrombotic mechanism of EH was that the nitrogen EPR short peptide of EH cleaved through FXIa and/or FXa, and the active metabolite hirudin was released at the microthrombus site, which inhibited activity of thrombin and the formation of new thrombus. Normally, EH had no antithrombotic activity due of low FXIa, and antithrombotic activity could only be produced when the coagulation system was activated.[17] This mechanism not only effectively inhibited thrombosis, but also significantly reduced bleeding side effects.

Activated partial thromboplastin time (APTT) was an important parameter to measure the therapeutic effect of hirudin and to change the therapeutic dose. Previous experiments had shown that hirudin significantly prolonged APTT, PT and TT, and the duration of APTT was positively correlated with the plasma concentration of hirudin.[26,27] In this study, the prolongation of APTT was only found in the single-dose trial of 0.2mg group (1 case) and continuous administration of 0.30mg/kg/h (2 cases) and 0.45mg/kg/h (2 cases). The APTT increase of the case in 0.2mg group was occurred on the 8th day after administration when over 7 half-life elapsed, therefore it was not related to the study drug. The prolongation of APTT

in the continuous administration all occurred on the day of injection, which could be related to the EH. However, they were all mild and recovered on the same day or the next day without any treatment. The slight prolongation of APTT suggested that a little of hirudin was released with the increase of EH loading, but the hirudin level in healthy subjects remained at a low level after continuous administration, indicating that EH was generally safe in healthy adults.

Furthermore, fibrin D-dimer increase and fibrinogen decrease were found in several cases during the study. Many studies[28-30]indicated that levels of D-dimer were typically elevated with acute VTE. However, D-dimer levels may also increase in a variety of nonthrombotic disorders such as lipemia, hyperbilirubinemia, and hemolysis. In hospitalized and other acutely ill patients commonly affected, D-dimer testing had less utility because of the high frequency of false-positive results. So the meaning of D-dimer increase in this study need to be further investigated in the next clinical study. The decrease of fibrinogen in this study was hard to explained with the mechanisms associated with a reduction in fibrinogen concentration: hemodilution, consumption, and degradation. However, the of fibrinogen decrease can be demonstrated by evaluation of D-dimer, the other fibrin degradation product[31-33].

4.2 Pharmacokinetics

EH showed predictable pharmacokinetics after administered intravenously, with exposures increasing proportionally with dose. The pharmacokinetics parameters of EH in healthy volunteers were almost consistent with those found in preclinical study of monkeys and rats.

The concentration of EH in serum reached the peak within 5 minutes after the end of injection, with exposures (AUC and Cmax) increasing proportionally with doses between 0.2˜2.0mg/kg in single-dose and 0.15˜0.45mg/kg/h (24h) in continuous administration. After intravenous administration, the EH was mainly distributed in the extracellular fluid with an apparent distribution volume of 402.7-615.2 ml/kg, which was independent of the dosage.

Preclinical animal studies suggested that renal excretion was a major excretion route of EH, and the excretion in urine accounted for 65.9% of the total dose by isotope labeling of ^{131}I. However, in this clinical study, the cumulative excretion rate in urine of prototype drugs plus hirudin only was less ten percent which indicated that EH produced other metabolites beside hirudin to excrete in urine. Indeed, excepting for EH and hirudin, the two major measurable metabolites in human urine after intravenous administration of EH we found that nine and ten metabolites were truncated at the C-terminal of EH and hirudin, respectively. This caused a successive reduction in amino acids at the C-terminus, which suggested the EH was metabolised to produce hirudin and other metabolites and that hirudin was metabolised to corresponding metabolites by the kidney[17]. These results suggested that metabolic pathway of EH in vivo was similar to that of hirudin.[18] Moreover, the pharmacokinetic parameters and excretion of EH were also similar with hirudin.[20]

The pharmacokinetic parameters of hirudin and recombinant hirudin had been characterised in healthy volunteers.[34] Native hirudin and recombinant hirudin undergo little, if any, hepatic metabolism. In the studies of hirudin, more than 70% of the drug was excreted unchanged in the urine within the first hour after intravenous administration, and 95% was eliminated after 5 hours.[25] After a single intravenous injection in healthy volunteers, both native hirudin and recombinant hirudin have rapid distribution phases. The a half-life($T_{1/2}$) in studies with healthy volunteers ranged from 0.15 to 1.24 hours. The maximum plasma concentration (Cmax) was 0.6 to 1.0 mg/L. The volume of distribution (Vd) of native hirudin and recombinant hirudin ranged from 8.9 to 17.2L.[34-36] These results suggested that EH was similar with hirudin in pharmacokinetic parameters.

The ratio of area under the curve of hirudin to EH was 4.0 +- 1.2%, indicating that a small amount of EH was cleaved into hirudin, resulting in the high safety and low bleeding potential of EH. In normal organisms, the levels of activated FXa and FXIa were low[37] in that EH mainly existed in intact form, and its active metabolite was very low. However, the relationship between the activity level of hirudin and EH under in vivo hypercoagulable state was not clear, and further study was needed to establish the dose-effect relationship of EH in patients.

Interestingly, no hirudin was detected in the plasma samples of the 0.30 mg/kg/h group of continuous administration, while there was no significant difference in the concentration of EH between plasma and serum, which indicated that the hirudin in the serum may come from the process of blood coagulation in vitro accompanying the activated coagulate factors.

Considering the small sample size, the clinical therapeutic effect of EH should be confirmed by a future phase II–III study.

4.3 Limitations

There were a few limitations to the conclusions that could be made from this study. Because subjects were healthy, the pharmacokinetic data collected represented the best case and did not include variability due to patient covariates. As the study was performed in a small number of subjects, conclusions related to safety can only be made for common adverse events, but not rare adverse events.

5 Conclusions

The results of this study showed that the EH had good tolerance and safety in Chinese healthy subjects, but the safety and pharmacodynamics of this drug need to be further studied in thrombotic patients. No dose-limiting toxicity occurred, no deaths, no serious adverse events and serious adverse reactions, no adverse events and adverse reactions leading to withdrawal, and most adverse reactions returned to normal without intervention. In summary, the tolerance and PK characteristics of EH support that phase II clinical trials of this drug is performed and the recommended doses of EH are: 4-11.2mg/kg, and the recommended way of administration is first intravenous bolus injection of 0.4mg/kg, and then the dose is maintained at 0.15-0.45mg/kg/h, intravenous drip.

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COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CONTRIBUTORS

Conception and design: Wu Chu-tse and Jin Ji-De

Operation of clinical experiments/acquisition of data: Liu Yu-Bin, Wang Mei-Xia, He Jia, Zhang Lin, Zhou Ying, Xia Xia

Analysis of pharmacodynamics: Dong Xiao-Na and Dou Gui-Fang

Analysis and interpretation of data: All authors.

Drafting the manuscript or revising it critically for important intellectual content: all authors.

DATA AVAILABILITY STATEMENT

The clinical data that support the findings of this study are available from the corresponding author, in agreement with Beijing Institute of Radiation Medicine, upon reasonable request.

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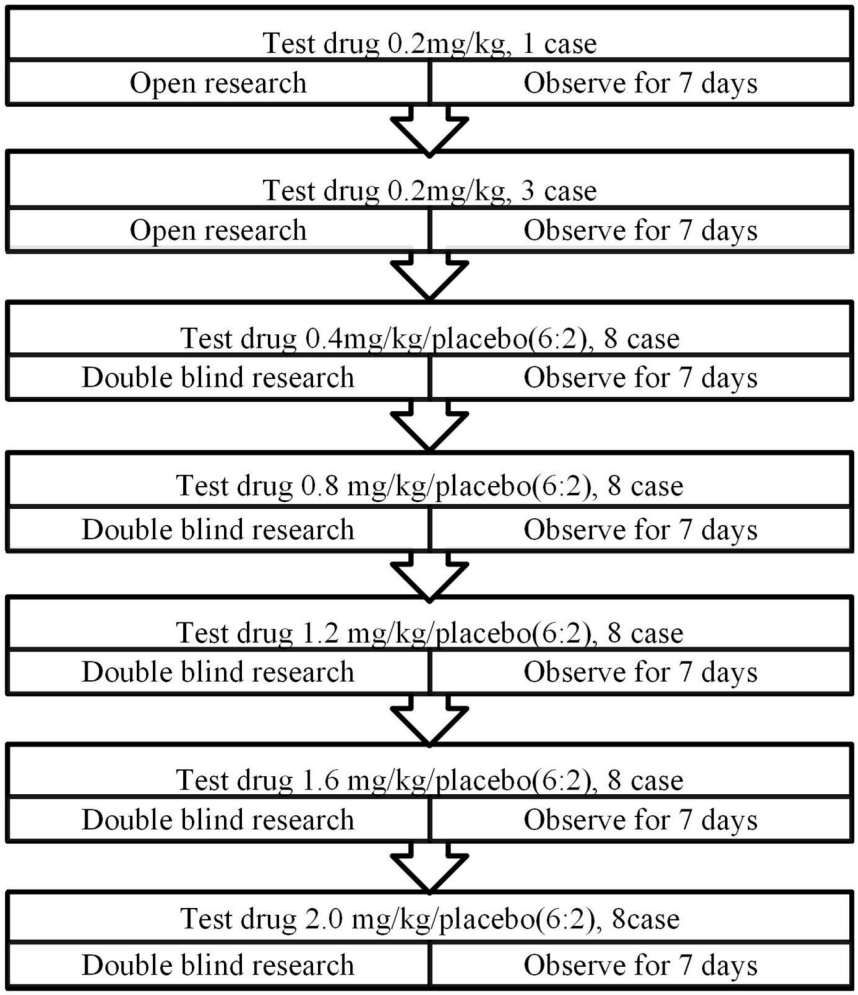

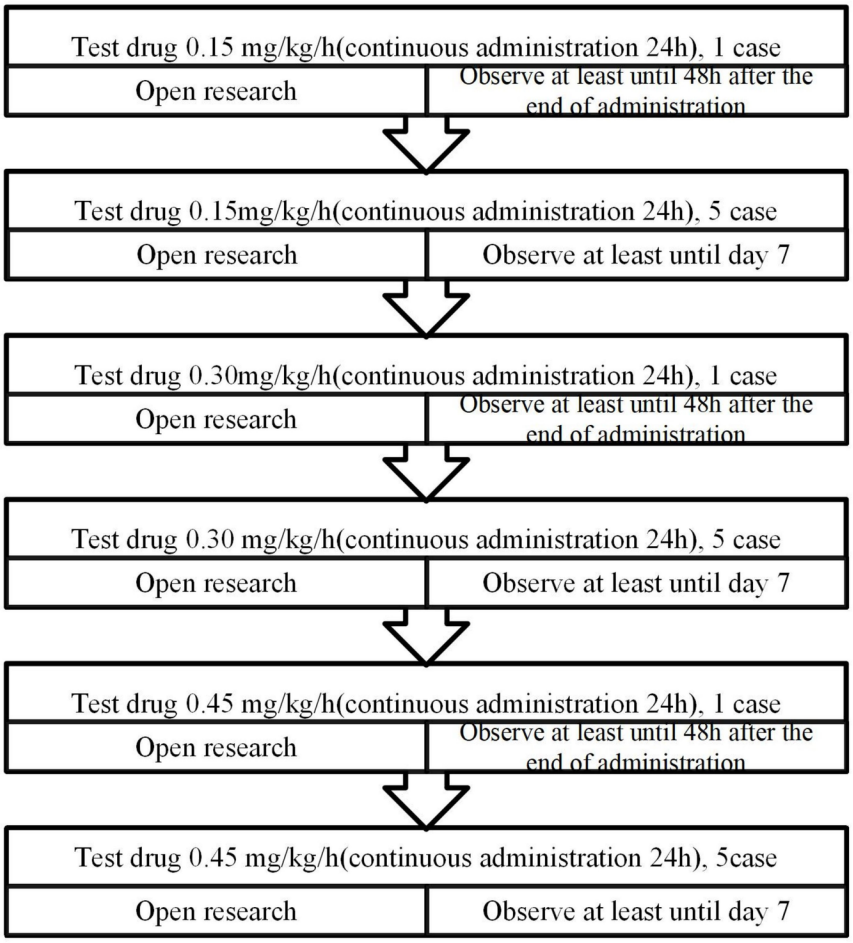

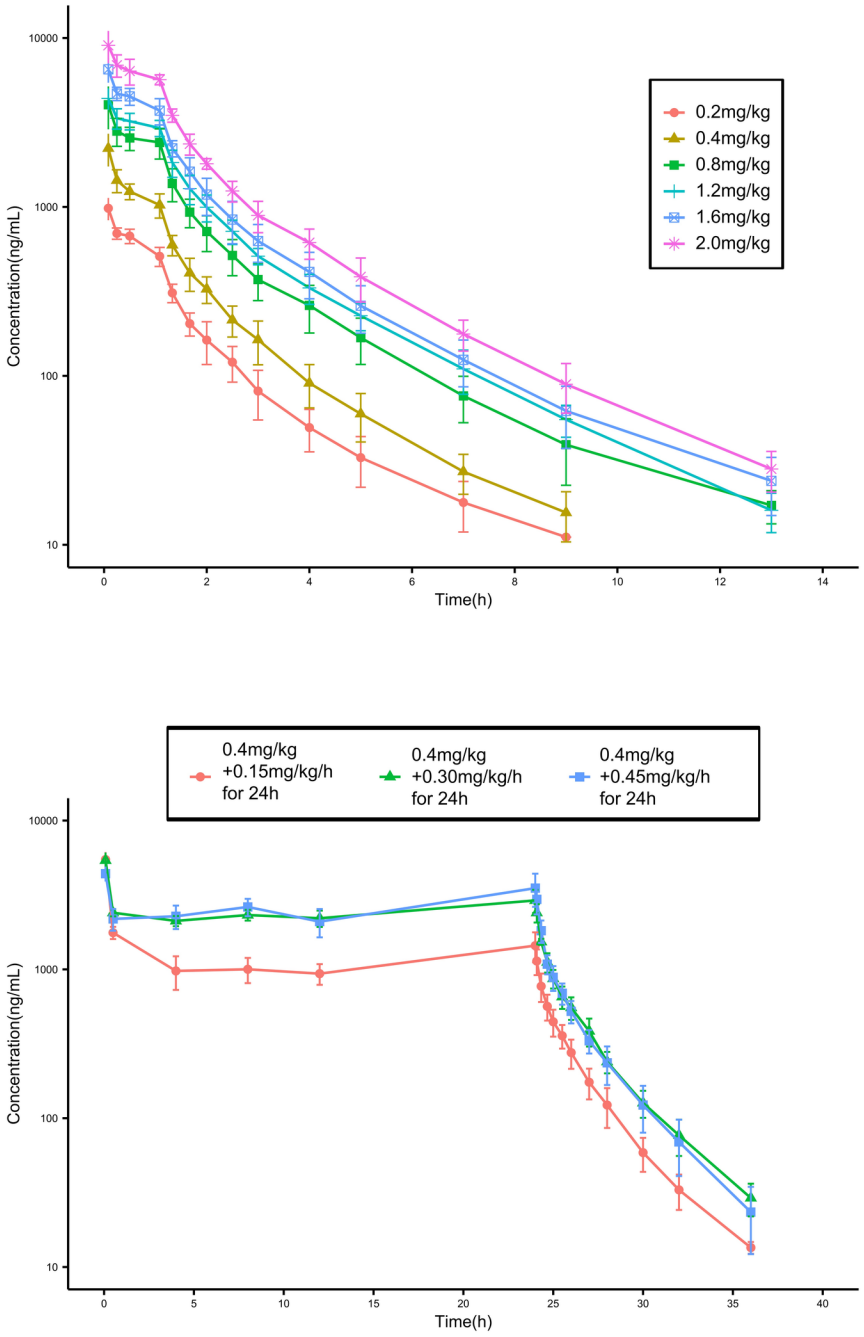

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