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Safety, tolerability and pharmacokinetics of phenoprolamine hydrochloride floating sustained-release tablets in healthy Chinese subjects

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ABSTRACT

The present study was designed to assess the safety, tolerability and pharmacokinetics of phenoprolamine hydrochloride floating sustained tablets (PHFST) in healthy Chinese subjects. 116 volunteers were randomized into single- or multiple-dose groups for oral administration 30–240 mg of PHFST once or 60–120 mg twice daily. Safety and tolerability were appraised by monitoring adverse events and laboratory parameters. Pharmacokinetics was assessed by determining the plasma concentrations of phenoprolamine hydrochloride with a validated HPLC method. In single-dose studies, no severe adverse events were observed in volunteers, and all adverse events were mild; the percentages of treatment-emergent events judged to be possibly related to the drug were 3/6 in the 240 mg dose group, 1/6 in the 180–210 mg dose groups, and none in the 30–150 mg dose groups; system exposure (AUC, C_{max}) increased with respect to dose at 30–120 mg, whereas AUC raised disproportionately with dose escalating from 120 to 240 mg; the absorption of phenoprolamine hydrochloride was unaffected by food. In multiple studies, no safety concerns were revealed up to 7 days; steady-state plasma concentration was achieved after approximately 4–5 days of repeated twice-daily dosing. PHFST is safe and well tolerated in healthy Chinese subjects. The mean C_{max} of PHFST is proportional to dose, but not the AUC. Oral dosing regimen selected for subsequent Phase II/III clinical trials was 60 mg of PHFST, b.i.d., and dose up to 120 mg, b.i.d. – may be used to achieve better antihypertensive effect.

1. Introduction

Uncontrolled hypertension is a major risk factor for stroke, coronary heart disease, left ventricular hypertrophy, arrhythmia, arteriosclerosis, end-stage renal disease and other life-threatening disorders. According to the World Health Organization, hypertension is the third leading cause of death worldwide. Current estimates indicate that 1000 million people worldwide, and 160 million in China, are living with high blood pressure, moreover, the numbers are rising (Berkow and Barnard, 2005; Chen et al., 2008). Today's attempts to bring high blood pressure down to normal level require a combination therapy with several classes of compounds. Numerous classes of antihypertensive agents are on the market, and considerations in the use of antihypertensive drug classes embrace diuretics, β-adrenergic antagonists, ACE inhibitors, angiotensin II antagonists, calcium channel blockers, as well as α-adrenergic antagonists/central acting agents (Carter, 2004; Heneghan et al., 2007; Stergiou and Salgami, 2004). This usually involves multiple visits to the doctor in order to adjust the relevant doses of these medicines. To confound this issue, patients would be not only suffering from hypertension, but also smarting from complications due to obesity, stroke and diabetes. These risks, therefore, make the need for exploiting more effective antihypertensive agents necessarily.

In recent years it has been demonstrated that 1-(2,6-dimethylphenoxyl)-2-(3,4-dimethoxyphenylethylamino) propane hydrochloride (phenoprolamine hydrochloride, seen in Fig. 1) possesses remarkably such an antihypertensive effect with mild toxicity (Lu et al., 2000; Ni et al., 1988; Qian et al., 1998; Qu et al., 2003; Xiong and Qian, 1997; Yuan et al., 2001; Zhang et al., 1998). Furthermore, compared with other drugs used in the treatment of hypertension, it has characteristic mechanism of highly selective α_1-adrenoceptor blocking action besides calcium antagonistic effect (He et al., 2008; Hu and Qian, 2001; Liu et al., 2002; Zhong et al., 2002). Had been accepted for Phase I clinical trial by the State Food and Drug Administration (SFDA) of China, phenoprolamine hydrochloride maybe exploited as a promising antihypertensive drug in clinical use, aiming at the effect mentioned above.

However, pharmacokinetic studies had indicated that the elimination half-life ($t_{1/2}$) of phenoprolamine hydrochloride regular tablets in beagles is very short and not suitable for the treatment of hypertension. In view of this characteristic, phenoprolamine

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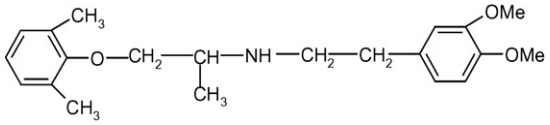

Fig. 1. Chemical structure of phenoprolamine hydrochloride.

hydrochloride floating sustained-release tablets (PHFST) were explored and manufactured (Xu et al., 2006). In this study, we evaluated the safety, tolerability and pharmacokinetics of PHFST in healthy Chinese subjects to provide evidence for further clinical trials.

2. Methods

The study was performed at the Institute of Clinical Pharmacology, Tongji Medical College, Huazhong University of Science and Technology. The study protocol conformed to all relevant regulatory requirement including the Declaration of Helsinki and Good Clinical Practice and were reviewed and approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology. Written informed consent was obtained from each subject before the study.

2.1. Subjects

Subjects (Han nationality, half male and half female) could be qualified to participate this study only when (1) their body mass index (BMI) was in 19–24 kg/m^2, (2) their age ranged from 19 to 45, and (3) they were determined to be in good health as assessed by their personal medical history, physical examination, and laboratory studies including blood biochemical test, routine blood and urine test, chest fluoroscopy, as well as electrocardiogram.

Subjects were excluded if they (1) had a history or clinical manifestations of significant metabolic, hematological, pulmonary, cardiovascular, gastrointestinal, neurologic, hepatic, renal, urological, or psychiatric disorders; (2) had a history of hypersensitivity or allergies to phenoprolamine hydrochloride or to any drug compound; (3) had a history of stomach or intestinal surgery, except appendectomy; (4) had a history or presence of an abnormal ECG that, in the investigator's opinion, was clinically significant; (5) had a history of alcoholism or drug addiction within 6 months prior to the study entry; (6) had participated in a clinical trial and received an investigational drug within 3 months prior to the start of the study; (7) had donated blood within the preceding 30 days; (8) had poor peripheral venous access; (9) used prescription or over-the-counter drugs within 1 week prior to study entry and during the study; (10) refused to abstain from the use of alcohol, caffeine, or grapefruit containing products 1 week prior to and throughout the study; and (11) had a positive urine drug test at the screening visit.

All volunteers provided written informed consent to participate in the trial. They were informed that the study was for research only, that the study was not expected to provide them with any therapeutic benefit, and that they were free to withdraw from the study at any time without prejudice.

2.2. Drugs and preparations

Phenoprolamine hydrochloride (99.5% pure) was provided by China Pharmaceutical University. PHFST (gastric floating preparation), 30 mg (batch no. 0041512) and 60 mg (batch no. 0041518), manufactured according to Good Manufacturing Practice, were from Hanhe Shiye Co. (Nanjing, Jiangsu Province, China).

2.3. Study design

2.3.1. Single-dose studies

A randomized, open-label, dose escalating study was conducted to assess the safety and tolerability of PHFST. 44 healthy subjects, half male and half female, were randomized into 30, 60, 90, 120, 150, 180, 210 and 240 mg dose groups (4–6 subjects in each) balanced by sex and body weight. The trial was designed to begin with the 30 mg dose group and would not proceed to the higher dose group until the safety and tolerability of the lower were confirmed. The subjects were required to fast overnight (10 h) before and for 4 h after administration yet water intake was allowed 2 h after administration.

36 healthy subjects were randomized into 30, 120, and 240 mg dose groups (12 subjects in each) for the pharmacokinetic profile, according to the results of safety and tolerability study. After an overnight fasting (10 h), each subject received the scheduled dosage with 250 mL of water. 2 h postdose, water intake was allowed 4 and 10 h postdose, low-fat standard meals were provided. Blood samples (3 mL) were collected at 0 (predose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h postdose. Plasma was separated, frozen and stored at −70 °C for analysis.

Another 12 healthy subjects were randomized into fasting and dining groups to assess the effect of food on the pharmacokinetics of PHFST, according to a double-period crossover design. All subjects were required to fast overnight (10 h), then a subgroup (six subjects) received 60 mg of PHFST under a fasting condition; another subgroup (six subjects) received 60 mg of PHFST 10 min postmeal. Intake of food and water was allowed the same way as described above, and blood samples were also collected at different time points. After a washout period of 7 days, the study was repeated once again.

2.4. Multiple-dose studies

12 healthy subjects, half male and half female, were randomized into 60 and 120 mg dose groups (six subjects in each). These subjects were given 60 or 120 mg of PHFST orally twice daily for 7 days to assess its safety and tolerability. Intake of food and water was allowed the same way as that in the single-dose study.

Another 12 healthy subjects were given 60 mg PHFST orally twice daily (at 7:30 AM and 19:30 PM) for 5 consecutive days for the assessment of its pharmacokinetic profile. Blood samples (3 mL) were collected prior to daily dosing on days 3–5 and after dosing the last dose of PHFST at specified times (0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16 and 24 h). Plasma was separated and kept the same way as that in the single-dose study.

2.5. Safety and tolerability

All subjects were kept in the study unit and continuously observed. Details of symptoms such as asthenia, headache, dizziness, nausea, vomiting, diarrhea and anepithymia were obtained through a daily questionnaire and recorded by the study physicians. Safety assessments such as physical examination, vital signs, electrocardiogram, routine blood and urine test, together with blood biochemical test were conducted before study and at the end of study. The blood biochemical test comprised of potassium (K^+), sodium (Na^+), chlorine (Cl^-), urea nitrogen (BUN), creatinine (Cr), alanine transaminase (ALT), aspartic transaminase (AST), total bilirubin (TBIL), fasting blood glucose (GLU), triglyceride (TG) and total cholesterol (CHOL) and high-density lipoprotein (HDL-C). Vital signs including body temperature, pulse, breathing rate and blood pressure (BP) were also assessed, respectively at 0.5, 1, 2, 4, 8, 12 and 24 h after administration in single-dose study and before administration daily in multiple-dose study.

Adverse events which occurred during the study, defined as mild (the event does not interfere with the usual activity of the subject), moderate (the event alters the usual activity of the subject or leads to a modification of dose of the test treatment) or severe (the event prevents any usual activity of the subject or needs the definitive stop of the test treatment), serious (the event results in death, is life threatening, requires subject hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or may require medical intervention to prevent the above outcomes) were recorded, assessed and reported according to Good Clinical Practice. The causality between the study drug and an adverse event, described as 'certainly', 'probably', 'possibly', 'suspected' or 'not related', was verified.

2.6. Drug analysis

Drug analysis was performed in lab of pharmacokinetics of the Institute of Clinical Pharmacology of Tongji Medical College. The plasma phenoprolamine hydrochloride concentration was determined by a validated HPLC method. Clonidine was selected as the internal standard. The plasma sample (1 mL) was pretreated by extraction with aether and the supernatant was evaporated to dryness. The residual was reconstituted with 100 μL mobile phase and 20 μL was injected into the HPLC system. The analysis was separated on a Hypersil C_{18} column (5 μm particle size, 4.6 mm × 200.0 mm) by isocratic elution with methanol:1% ammonium acetate (99.7:0.3, v/v) at a flow rate of 1.0 mL/min and analyzed by a PDA detector at 230 nm. The analysis of blank plasma indicated no interference of endogenous components with phenoprolamine hydrochloride in final extract. The weighted ($1/x^2$) calibration curve was linear over the plasma concentration range of 5–1000 ng/mL with a correlation coefficient (r) of 0.9967. The lowest limit of quantification for phenoprolamine hydrochloride was 5 ng/mL; the mean inter-day and intra-day precision (RSD) fell in the range of 3.00–8.71% and 3.61–8.43%, respectively; the mean method recoveries were 90.06–102.23% and the mean extraction recoveries from plasma were 81–84%. The samples were determined once, although those in doubt were re-analyzed.

2.7. Pharmacokinetic calculations

The mean concentrations of phenoprolamine hydrochloride in plasma at each time point were determined by averaging data and the pharmacokinetic parameters were calculated by Drug and Statistic (DAS) software (version 1.0; Rui-yuan Sun, Wuhu, Anhui Province, China). The maximum concentration (C_{max}) and corresponding peak time (T_{max}) of phenoprolamine hydrochloride was determined by the inspection of the individual drug plasma concentration–time profiles. The elimination rate constant (K_e) was obtained from the least-square fitted terminal log-linear portion of the plasma concentration–time profiles. The elimination half-life ($t_{1/2}$) was calculated through $0.693/K_e$. The area under the plasma concentration–time curves of phenoprolamine hydrochloride, from time zero to infinity ($AUC_{0-\infty}$) was determined by the trapezoidal rule to the last measurable concentration (C_t) plus the additional area from time t to infinity, calculated as C_t/K_e.

The mean steady-state concentration ($\bar{C}_{ss}$) and the degree of fluctuation (DF) was calculated as $AUC_{0-\tau}/\tau$ and $(\bar{C}_{ss}^{max} - \bar{C}_{ss}^{min})/C_{ss}$, respectively.

2.8. Statistical analysis

The statistical software of SPSS 12.0 was used to perform statistical analysis. A P-value of <0.05 was considered significant.

Analysis of safety included descriptive summaries of baseline characteristics, procedural data, and all the other safety variables, including adverse events, terminations, vital signs, and clinical laboratory results. The values obtained before and after administration in single- and multiple-dose studies were analyzed by paired t–t-test and the variances among groups in the single-dose were analyzed by analysis of variance (ANOVA). Adverse events were summarized with frequencies and percentage.

AUC, MRT, MAT, T_{max}, C_{max} and $t_{1/2}$ were estimated for pharmacokinetic profiles. Statistical comparisons of these pharmacokinetic parameters among different doses, as well as single- to multiple-doses were performed by analysis of variance (ANOVA). The variances between fasting and dining groups were compared by a paired t–t-test.

3. Results

3.1. Study population

The baseline characteristics of the study population are presented in Table 1. Treatment groups were well balanced in terms of sex and weight.

3.2. Safety and tolerability

Overall, PHFST was well tolerated at doses up to 240 mg administered once and at doses up to 120 mg administered twice daily for 7 days. No severe adverse events occurred during the study and all subjects were in good compliance; no symptoms or signs were observed.

All laboratory abnormalities, which were judged to be possibly related to the study drug, were mild and tolerable, and did not lead to discontinuation of the study; recovery was without treatment. No changes of clinical significance were found in routine blood and urine tests. In the single-dose study, high TBIL concentrations were found in one subject of the 210 mg dose group and in three subjects of the 240 mg dose group. But in the multiple-dose study, increases in TBIL concentration were not found. In the single-dose study, one subject receiving PHFST at 180 mg had a prolonged QT_c interval, which was 457 ms, but no subject receiving PHFST at higher single- or multiple-dose had a prolonged QT_c interval (450 ms for males and 470 ms for females) at any study assessment.

Number of subjects with adverse events and number of adverse events after single- or multiple-doses of PHFST were shown in Table 2.

Table 1
Characteristics of study population.

	Single-dose (mg)								Multiple-dose (mg)	
	30	60	90	120	150	180	210	240	60	120
Sex (female/male)	2/2	2/2	3/3	3/3	3/3	3/3	3/3	3/3	3/3	3/3
Age (years)	23.0 ± 1.4	22.8 ± 1.5	23.2 ± 1.7	25.8 ± 2.6	21.3 ± 0.8	22.5 ± 0.6	23.0 ± 2.3	24.8 ± 2.3	22.0 ± 1.4	22.3 ± 1.0
Height (cm)	164 ± 6	167 ± 7	165 ± 8	167 ± 9	167 ± 7	167 ± 8	167 ± 9	167 ± 4	165 ± 6	165 ± 8
Weight (kg)	60 ± 7	61 ± 8	56 ± 8	61 ± 7	57 ± 7	55 ± 4	58 ± 9	56 ± 4	54 ± 4	57 ± 9
BMI (kg/m^2)	22.1 ± 1.2	21.5 ± 1.8	20.5 ± 1.9	22.0 ± 0.8	20.4 ± 1.4	20.8 ± 0.7	20.8 ± 1.8	20.8 ± 0.8	19.9 ± 0.7	20.9 ± 1.6

Table 2
Number of subjects with adverse events and number of adverse events after single- or-multiple-doses of PHFST.

Treatment	Single-dose (mg)								Multiple-dose (mg)	
	30	60	90	120	150	180	210	240	60	120
Number of subject treated	4	4	6	6	6	6	6	6	6	6
Number of subjects with adverse events	0	0	0	0	0	1	1	3	0	0
Number of adverse events										
Mild	0	0	0	0	0	1	1	3	0	0
Moderate	0	0	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	1	1	3	0	0

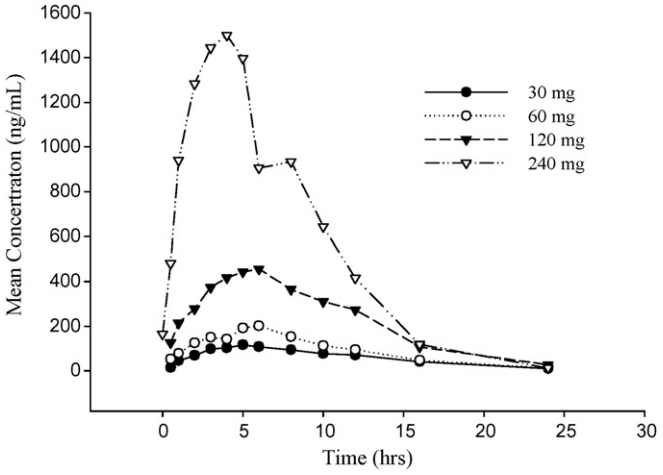

Fig. 2. Mean plasma concentration–time profiles of phenoprolamine hydrochloride after oral administration of 30, 60, 120 and 240 mg PHFST ($n = 12$).

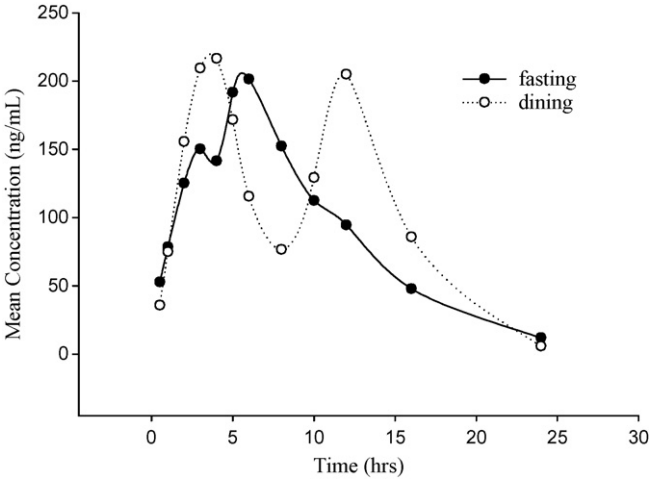

Fig. 3. Mean plasma concentration–time profiles of phenoprolamine hydrochloride after oral administration of 60 mg PHFST in fasting and dining conditions in healthy volunteers ($n = 12$).

Because of the antihypertensive effect of PHFST, changes in blood pressure (BP) were closely monitored. In the single-dose study, BP reduced in 17 volunteers of the 44 subjects. The range of reduction of systolic BP was 12–20 mmHg and the range of reduction of diastolic BP was 2–10 mmHg. But there was no symptoms related with the reduction of BP in these subjects. The largest reductions in BP were observed during 0.5–4 h after administration.

3.3. Pharmacokinetic profile

3.3.1. Single-dose pharmacokinetic study

The plasma concentration–time curves of phenoprolamine hydrochloride are summarized in Fig. 2. Plasma concentrations of phenoprolamine hydrochloride were generally measurable at all time points postdose. Individual maximum concentrations ranged from 154.89 ng/mL (at 30 mg) to 1753.74 ng/mL (at 240 mg). Pharmacokinetic parameter values estimated by noncompartmental procedures are presented in Table 3. The relationship between extent of systemic exposure to phenoprolamine hydrochloride and dose was characterized by the mean AUC and C_{max} values. Following a single administration of 30–240 mg PHFST, there was an approximately dose-proportional increase in C_{max} values, whereas AUC increased with respect to dose at 30–120 mg PHFST, but when the dose escalating from 120 to 240 mg, AUC increased disproportionately, which indicated nonlinear pharmacokinetic profile. Plasma concentrations of phenoprolamine hydrochloride declined with an approximate mean apparent terminal half-life of 5–7 h following administration. The mean values of the MRT ranged from 7.67 to 8.54 h. In addition, $t_{1/2}$ and MRT were both independent of the dose.

3.4. Effect of food on phenoprolamine hydrochloride pharmacokinetics

Comparison of the mean concentration–time curves of oral administration PHFST in fasting and dining conditions is shown in

Table 3
Pharmacokinetic parameters of PHFST in 48 human volunteers after administration of four doses ($n = 12$, $\bar{x} \pm s$) in fasting condition and dining condition.

Parameters	Fasting condition				Dining condition
	30 mg group	60 mg group	120 mg group	240 mg group	60 mg group
AUC_{0-24} (ng h/mL)	1424.99 ± 675.61	2224.99 ± 1536.63	5333.81 ± 2962.91	16800 ± 10918	2521.57 ± 1876.62
$AUC_{0-\infty}$ (ng h/mL)	1428.00 ± 675.38	2228.33 ± 1535.36	5335.72 ± 2962.12	16802 ± 10918	2522.53 ± 1876.77
MRT_{0-24} (h)	8.54 ± 1.76	7.73 ± 1.66	7.89 ± 1.38	7.67 ± 2.22	7.66 ± 3.79
$MRT_{0-\infty}$ (h)	8.58 ± 1.73	7.76 ± 1.67	7.90 ± 1.37	7.67 ± 2.22	7.67 ± 3.79
MAT (h)	2.02 ± 1.28	1.68 ± 0.94	1.84 ± 1.30	1.36 ± 1.03	0.98 ± 0.53
T_{max} (h)	6.42 ± 3.29	5.67 ± 2.06	5.33 ± 2.10	5.33 ± 2.02	7.08 ± 4.19
C_{max} (ng/mL)	154.89 ± 49.09	252.39 ± 136.22	538.27 ± 275.18	1753.74 ± 829.73	407.55 ± 222.12
$t_{1/2}$ (h)	4.76 ± 2.89	4.92 ± 1.88	3.76 ± 1.28	3.96 ± 2.06	2.48 ± 1.34

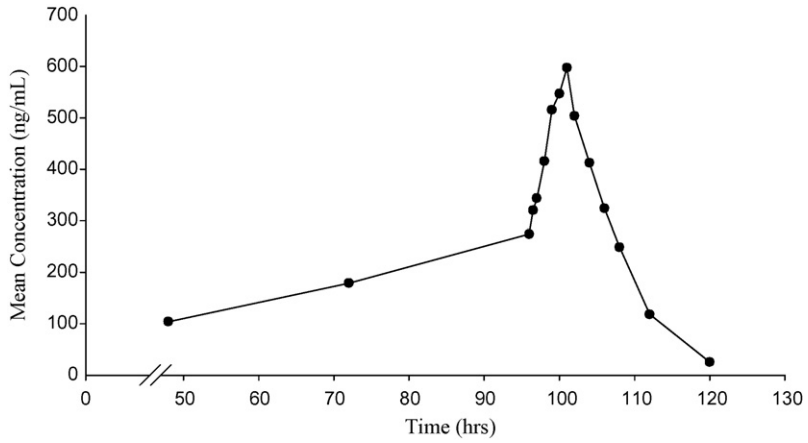

Fig. 4. Mean plasma concentration–time profiles of phenoprolamine hydrochloride after oral administration of 60 mg PHFST for 5 days, b.i.d. ($n = 12$).

Fig. 3. The mean concentration–time curves in dining condition displays conspicuous two peaks, whereas that is not obvious in fasting conditions. The main pharmacokinetic parameters of oral administration PHFST in fasting conditions and in dining conditions are presented in Table 3. No statistical significance of the pharmacokinetic parameters was found in the fasting and dining groups by ANOVA, except for MAT ($P < 0.05$), indicating that food did not affect the extent but the rate of absorption of phenoprolamine hydrochloride after oral dosing.

3.5. Multiple-dose pharmacokinetic study

Assessment of steady-state was undertaken by comparing predose plasma phenoprolamine hydrochloride concentrations (trough concentrations, C_{min}), for which the samples were collected on days 3–5. The obtained C_{min} on days 3–5 was 104.01 ± 131.85, 179.24 ± 213.80 and 274.57 ± 260.91 ng/mL, respectively. ANOVA analysis showed no difference between the latter two ($P > 0.05$), indicating that phenoprolamine hydrochloride appeared to attain steady-state levels after approximately 4–5 days of repeated twice-daily dosing. The mean plasma concentration–time curves of phenoprolamine hydrochloride following multiple-doses of PHFST 60 mg continuously for 5 days is shown in Fig. 4 and main pharmacokinetic parameters are shown in Table 4. The value of AUC_{SS} was 4961.03, whereas that was 2224.99 in the same dose of single-dose study, indicating that phenoprolamine hydrochloride accumulation was greater than that predicted from the single-dose data. The mean DF was 0.98, indicating that the difference between peak level and trough concentration was small and plasma phenoprolamine hydrochloride concentration was steady. The half-life value, calculated from the observed accumulation of phenoprolamine hydrochloride, was similar to those in single-dose study, suggesting that the elimination of phenoprolamine hydrochloride was time dependent.

Table 4
Pharmacokinetic parameters following multiple-doses of PHSFT 60 mg continuously for 5 days, b.i.d. ($x \pm s$, $n = 12$).

Parameters	60 mg for consecutive 5 days, b.i.d.
AUC_{ss} (ng h/mL)	4961.03 ± 2767.22
C_{max} (ng/mL)	637.55 ± 312.17
C_{min} (ng/mL)	248.93 ± 163.03
C_{ss} (ng/mL)	412.42 ± 230.60
T_{max} (h)	4.17 ± 0.94
DF	0.98 ± 0.38
$t_{1/2}$ (h)	3.52 ± 1.25

4. Discussion

Phenoprolamine hydrochloride is a newly synthesized agent, which has highly selective α_1-adrenoceptor blocking action besides weak calcium antagonistic effect, and maybe exploited as a promising antihypertensive drug in clinical use. In this study, we evaluated the safety, tolerability and pharmacokinetic profile of single and multiple oral dosing regimens of its sustained-release tablets, PHFST, in healthy Chinese volunteers.

In the safety and tolerability study, although the reduction of BP was commonly observed, symptoms of postural hypotension were not reported by any subject during the study. High TBIL concentrations were found in four subjects at dose of 210 and 240 mg, but they were all mild. The causality between the drug and an adverse event was described as “probability”. The effect of PHFST on TBIL and ECG may be considered in further studies to evaluate. We observed an isolated incident of QT_c interval prolongation in one subject at 180 mg group. The absolute value was 457 ms. It was sporadic and not related to dose. Nevertheless, this finding suggests that the compound may have the potential to prolong the QT_c interval and warrants further investigation. No severe adverse events were observed in this study. A favorable tolerability profile was also observed in subjects receiving continuously dose PHFST for 7 days. In conclusion, PHFST was well tolerated in subjects with dose up to 240 mg once daily or with dosed up to 120 mg twice daily for 7 days.

PHFST exhibited good absorption properties, with peak concentrations appearing 5–7 h after dose administration. Plasma concentrations of phenoprolamine hydrochloride were generally measurable 24 h postdose. Noncompartmental analysis in healthy subjects indicates linear pharmacokinetic behavior with respect to dose at 30–120 mg of PHFST, whereas nonlinear pharmacokinetic profile was observed when the dose escalated progressively to 240 mg. The nonlinear pharmacokinetics of phenoprolamine hydrochloride may possibly be explained by the partial saturation of hepatic first-pass metabolism (Ding et al., 2001a,b). There was also wide intersubject variability in pharmacokinetic parameters, particularly the AUC, so the mean profiles should be interpreted with care. After multiple dosing, phenoprolamine hydrochloride accumulation was greater than that predicted from the single-dose data. Steady-state levels were achieved by the 4–5 days of multiple dosing. Food did not affect the extent but the rate of absorption of phenoprolamine hydrochloride after oral dosing. The mean concentration–time curves under dining condition shows two peaks under dining condition and this may possibly be explained by the gastric floating preparation. In both single and multiple studies, the values of terminal half-life were independent of the dose.

Recommended Phase II/III dosing schedule was administered at initial dose of 60 mg twice daily and dose of PHFST up to 120 mg twice daily may be used if the antihypertensive effect of PHFST is not obvious.

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