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Short communication

Development and validation of a sensitive U-HPLC–MS/MS method with electrospray ionization for quantitation of ranolazine in human plasma: Application to a clinical pharmacokinetic study

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ABSTRACT

A simple, sensitive and high-throughput ultra high-performance liquid chromatography electrospray ionization mass spectrometry (U-HPLC–ESI-MS/MS) method has been developed and validated for the determination of ranolazine in human plasma. Propafenone was employed as the internal standard (I.S.). The analytes were chromatographically separated on a BEH C_{18} column (50 mm × 2.1 mm, 1.7 μm) with a mobile phase consisting of acetonitrile and aqueous ammonium acetate solution (0.06% formic acid, 7.5 mmol L^{-1} ammonium acetate, 40:60, v/v). Detection of the analytes was achieved using positive ion electrospray ionization via multiple reactions monitoring mode. The mass transitions were m/z 428.3 → 279.3 for ranolazine and m/z 342.4 → 115.9 for propafenone. The assay was linear over the concentration range 1–3000 ng mL^{-1}, with correlation coefficients ≥0.997. The intra- and inter-day coefficients of variation were less than 8.9% in terms of relative standard deviation and accuracy ranged from 93.0 to 108.9% at all quality control levels. The validated method was a simple sample preparation procedure and short run-time (<2.0 min) method, which was successfully applied to a phase I pharmacokinetic study of ranolazine in Chinese healthy volunteers.

1. Introduction

Ranolazine (Fig. 1), (±)-N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy) propyl]-1-piperazine acetamide is a novel compound that is approved by the US FDA in January 2006 for the treatment of chronic angina pectoris in combination with amlodipine, β-adrenoceptor antagonists or nitrates, in patients who have not achieved an adequate response with other anti-anginals [1,2]. Ranolazine is the first approved agents from a new class of anti-anginal drug in almost 25 years, unlike existing anti-ischemic agents, studies with ranolazine had shown it to be hemodynamically neutral, with little effect on blood pressure and heart rate [3].

Since ranolazine lacks strong characteristic UV absorption, a HPLC–UV detection method does not provide suitable sensitivity and selectivity for the determination of ranolazine in biological samples [4,5]. Recently, two LC–MS methods with selected ion monitoring (SIM) have been published [6,7]; both of them allowed the quantitation of ranolazine in rat plasma with the lower limit of quantitation (LLOQ) above 20 ng mL^{-1} and relatively long HPLC/MS analysis time (6 or 7 min per sample) [8]. Although LC–MS/MS methods have been reported for the analysis of ranolazine in plasma, but the lower limit of quantitation can not meet the requirements for our pharmacokinetic studies and also sample pre-treatment procedure with solid-phase extraction (SPE) procedure or liquid–liquid extraction was time-consuming [9–11]. Recently, the ultra-performance LC (U-HPLC) has been introduced and quickly adopted in quantitative analysis of biological matrix. The van Deemter equation indicates that, as the particle size decreases to less than 2.5 μm, there is a significant improvement in efficiency that will not reduce with increased LC flow rates. Compared with conventional HPLC columns, U-HPLC, by utilizing 2.5 μm particle, greatly increased the separation throughput and efficiency, resulting in LC peaks as narrow as or less than 2 s [12].

According to the report, after a single oral dose of 500 mg ranolazine tablet in 48 h, the mean plasma concentration of ranolazine was about 2.5 ng mL^{-1}. In addition, plasma levels of ranolazine can vary widely between individuals. It was essential to establish an assay capable of quantifying ranolazine at concentrations down to 1.0 ng mL^{-1} for evaluation and interpretation of

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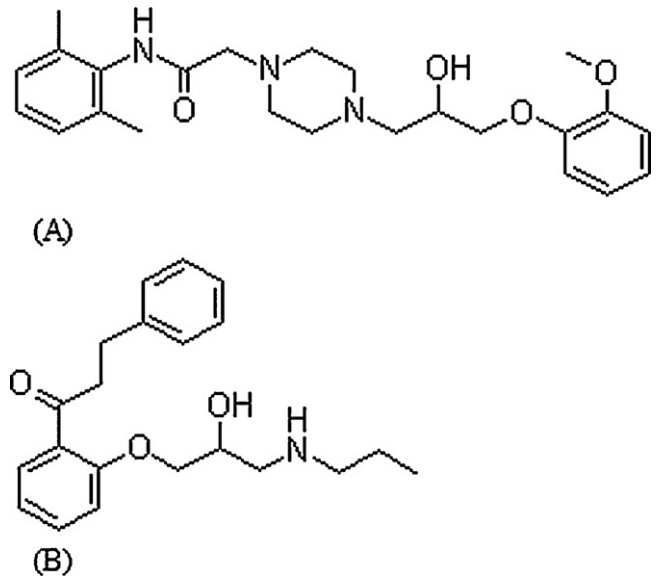

Fig. 1. Chemical structures of ranolazine [(A) MW: 427.54, (±)-N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazine acetamide] and IS [(B) propafenone, MW: 341.45, 1-[2-[2-hydroxy-3-(propylamino)propoxy]phenyl]-3-phenylpropan].

pharmacokinetic data. In our study, a simple, rapid (RT = 2.0 min), low LLOQ (1.0 ng mL^{-1}) and small injection volume (3 μL), sensitive U-HPLC–ESI-MS/MS method was developed. Following validation, this method was successfully applied to phase I pharmacokinetic studies of ranolazine performed to assess and compare the PK properties of ranolazine after administration of single oral doses (500, 1000 and 1500 mg) in healthy Chinese volunteers.

2. Materials and methods

2.1. Chemicals and reagents

Ranolazine pharmaceutical product (purity >99.3%) and Ranolazine 500 mg sustained-release tablets were provided by Fujian Tianquan Pharmaceutical Holdings Co., Ltd. (Longyan, People's Republic of China). Ranolazine, the reference standard (purity >99.3%), and the internal standard, propafenone hydrochloride (purity >99.9%), was purchased from the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, People's Republic of China). HPLC-grade acetonitrile were purchased from Merck KGaA (Darmstadt, Germany). Formic acid and ammonium acetate, also of HPLC grade, were obtained from Tedia Company, Inc. (Fairfield, Ohio). Distilled water was deionized by using a Milli-Q Gradient system A10 (Millipore, Bedford, MA, USA) and was used throughout the study.

2.2. Instrumentation

The U-HPLC–MS/MS system (Waters Corporation, Milford, Massachusetts) consisting of an acquity ultra high performance LC and electrospray ionization tandem mass spectrometer (U-HPLC–ESI-MS/MS; Quattro Premier XE, Waters Corporation) Chromatographic analysis of ranolazine and propafenone (I.S.) were performed on a Waters Acquity U-HPLC^{TM} BEH C_{18} column (50 mm × 2.1 mm, i.d., 1.7 μm particle size). All data were acquired employing MassLynx V4.1 Quantitative Analysis version analyst data processing software.

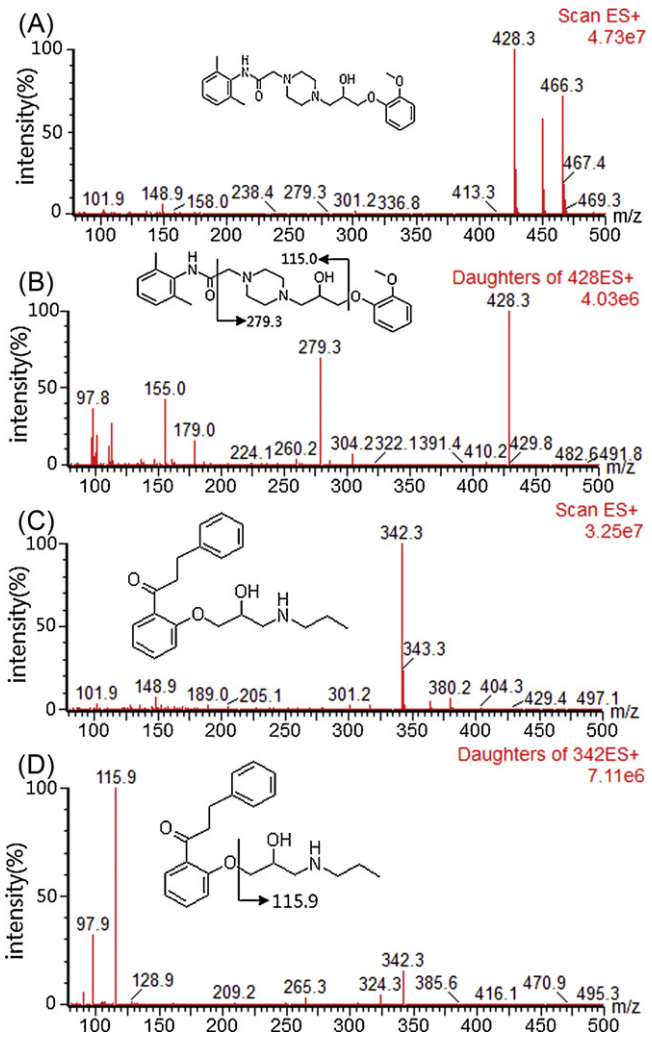

Fig. 2. The precursor and product ion scan mass spectra of ranolazine and the internal standard, propafenone. (A) Precursor ion scan mass spectra of ranolazine and (B) product ion scan mass spectra of ranolazine. (C) Precursor ion scan mass spectra of propafenone and (D) product ion scan mass spectra of propafenone.

2.3. U-HPLC–ESI-MS/MS conditions

The mobile phase composition was a mixture of acetonitrile–water containing (0.06% formic acid, 7.5 mmol L^{-1} ammonium acetate) in a ratio 40:60 (v:v). Measurements were made at a flow rate 0.35 mL/min at 40 °C column temperature. Mass spectrometric detection was performed on a U-HPLC–MS/MS system (Waters Corporation, Milford, Massachusetts) using multiple reaction monitoring (MRM). A turbo electrospray interface in positive ionization mode was used. The main working parameters of the mass spectrometer are summarized as follows: capillary voltage was 0.7 kV, the ionization sources and the desolvation temperature were 120 °C and 400 °C, respectively; desolvation gas flow rate was 750 L/h; the Ar gas was used for collision activated dissociation in Q2; the optimized collision cone voltage for the analyte and I.S. were 38 and 35 eV, and the optimized collision energies chosen for the analyte and I.S. were 24 and 22 eV, respectively. Fig. 2 shows the product ion mass spectra of $[M+H]^+$ of the analyte and I.S.

2.4. Sample preparation

Frozen human plasma samples were thawed at ambient temperature, 100 μL of the plasma sample was added to 200 μL

precipitation (acetonitrile solution of I.S.). After a thorough vortex mixing in a microcentrifuge tube for 2 min, the mixture was centrifuged at 12,000 rpm at 4 °C for 5 min; 100 μL of the upper layer was transferred to an injection bottle, which was loaded into autosampler cabinet and 3 μL aliquot was injected into the U-HPLC–MS/MS system.

2.5. Preparation of the stock and standard solutions

The stock solutions of ranolazine (100 μg mL^{-1}) and the internal standard (442 μg mL^{-1}) were separately prepared in 50% acetonitrile, respectively. The stock solutions were further individually diluted with the same diluents to give working standard solutions of both agents. All stock solutions were stored at 4 °C when not in use.

2.6. Preparation of calibration curves and quality control samples

Calibration standards of ranolazine were prepared at the concentration levels of 0, 1, 5, 10, 30, 100, 300, 900 and 3000 ng mL^{-1} by spiking an appropriate amount of the standard solutions in 100 μL blank plasma. The calibration curve was prepared and assayed along with quality control (QC) samples. QC samples were prepared in 100 μL blank plasma at three levels of 5, 200 and 2400 ng mL^{-1}, and stored at −20 °C.

2.7. Method validation

The selectivity of the method was measured by analysis of six blank plasma samples of different origin for interference at the retention times of the analyte and I.S. A calibration curve was constructed from a blank sample (a plasma sample processed without the I.S.) and eight non-zero samples covering the total range of 1–3000 ng mL^{-1}. The calibration curves were generated using the ratio of the peak area of ranolazine to the I.S. vs the concentration of ranolazine with a weight ($1/C^2$) factor. The LLOQ was defined as the concentration of the lower concentration standard in the calibration curve that was analyzed with accuracy within ±15% and a coefficient of variance ≤ 15%[13,14]. In order to assess the intra- and inter-day coefficients of variance and accuracy, the complete analytical runs were performed on the same day and on three consecutive days.

The extraction recoveries of ranolazine at three QC levels were determined by comparison of the peak areas of ranolazine extracted from plasma samples with that of ranolazine dissolved in post-extraction spiked blank human plasma samples. The matrix effect at three QC levels was determined by comparison of the peak areas of ranolazine dissolved in reconstitution solution (the final solution of blank plasma after protein precipitation and reconstitution) with that of ranolazine dissolved in mobile phase solution. Stability tests were performed for analyte-spiked plasma samples under various conditions: short-term storage (at ambient temperature), through freeze/thaw cycles (four cycles), and for long-term storage (frozen for 60 days), autosampler storage (at ambient temperature) by analyzing five replicates at low, medium and high QC concentrations.

2.8. Pharmacokinetic study

The validated method was applied to evaluate the pharmacokinetics of ranolazine. The study was assigned to open-label, randomized-sequence, 3 × 3 latin square design which consisted of three 1-day treatment periods and two 7-day washout periods. Twelve healthy Chinese volunteers were enrolled and completed the trial. The demographic data for these volunteers were mean age 24.7[1.6] years and mean weight 61.3[6.4] kg. Volunteers were hospitalized at 9:00 pm the night before the study and fasted 10 h before drug administration. Volunteers were randomly administered orally a single dose of 500, 1000, or 1500 mg of ranolazine (sustained-release tablets) with 250 mL of water at 8:00 am under fasting conditions. Sequential blood samples (4 mL each) were collected from an indwelling venous catheter (anticoagulated with sodium heparin) at 0 h (before administration) and 0.5, 1.0, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, and 48.0 h after administration. The blood samples obtained were frozen at −80 °C until analysis. The pharmacokinetics of ranolazine were evaluated. The maximum plasma concentration (C_{max}) and the time to reach it (T_{max}) were noted directly. PK analysis was performed using the pharmacokinetics program authorized by the Chinese Pharmacology Society (version 2.0, 2009, Beijing, China). Pharmacokinetic parameters were estimated based on plasma concentration–time data using a noncompartmental model. SPSS version 13.0 (SPSS Inc., Chicago, IL) was used for statistical analysis.

The protocol of this study was approved by the Ethical Committee of Second Xiangya Hospital of Central South University (Changsha, China). All participants signed a written informed consent after they had been informed of the nature and details of the study.

3. Results

3.1. Selection of the I.S.

It is important to choose the appropriate internal standard to achieve acceptable method performance, especially with U-HPLC–MS/MS, where matrix effects can lead to poor analytical results. We attempted different internal standard (tramadol, aripiprazole and phenoprolamine hydrochloride) reported in the literature and found they can not meet the needs of our experiment well, therefore, we tried many other substances and found that propafenone satisfied our study requirement, as it was easily commercially available. In addition, the behavior of its chromatography is similar to that of ranolazine. Clean chromatographs were obtained and no significant direct interference in the MRM channels at the relevant retention times was observed. In recent years, there is general consensus that isotope labeled versions of the drug are the ideal internal standards and it is possible to compensate for variability in extraction and ionization, such as ranolazine-d3 and ranolazine-d8. In the future, we should consider isotopic internal standard to be used in our experiments.

3.2. U-HPLC–MS/MS conditions

A specific, reliable and sensitive method to determine ranolazine concentration had been established. The U-HPLC–MS/MS with ESI positive ionization and the MRM mode provided a highly selective method for the determination of ranolazine and the I.S. Our studies compared MRM mode with select ion monitoring (SIM) mode, the results revealed that some endogenous substances in plasma interfered the determination of analytes when using SIM mode. While with MRM mode, a pure background had been obtained with less interference. The ESI positive ion mode was chosen for ion product since there are three hetero-N atoms in the structure of ranolazine. From full-scan mass spectrum via the first quadrupole (Q1) mass filter, the $[M+H]^+$, at m/z 428.3 for ranolazine and m/z 342.4 for I.S. were chosen as the precursor ion. By introducing those $[M+H]^+$ ions into the second quadrupole (Q2) cell with the optimum collision energy, the MS/MS fragmentation was achieved. After the dissociation via the Q3 mass filter, the most abundant ions in the product ion mass spectrum at m/z 279.3 for ranolazine and m/z 115.9

for I.S. were monitored for quantification. Full-scan product ion mass spectrum of ranolazine and I.S. are shown in Fig. 2. As the $[M+H]^+$ MRM transition at m/z 428.3 → 279.3 for ranolazine and m/z 342.4 → 115.9 for I.S. were the most intense ones, thus were used as the quantifier. Various mobile phase combinations of ammonium acetate in water and methanol or acetonitrile were investigated to optimize sensitivity, speed and peak shape. The results (data not shown) demonstrated that acetonitrile gave a better response than methanol, and the ammonium acetate (7.5 mmol L^{-1}) in water containing 0.06% formic acid not only regulate the PH of mobile phase and improved peak shapes but also promote ionization of the analytes in the ESI^+ mode, at the same time, increase the sensitivity. In this study, we utilized a relatively simple method of protein precipitation to prepare the blood sample, which was a small solvent consumed procedure. As demonstrated in this method, it was perfectly suitable for a high-through put routine such as pharmacokinetic studies.

3.3. Selectivity

The specificity of the method was investigated by screening six different batches of blank plasma. The typical chromatograms of blank plasma, spiked in the mobile phase with ranolazine and the I.S., spiked plasma sample with ranolizine and the I.S., and the plasma sample from a volunteer after oral administration are shown in Fig. 3. The retention times of ranolazine and I.S. were 1.01 and 1.82 min, respectively.

3.4. Linearity, extraction recovery, precision, accuracy and limit of quantification

The standard curves for ranolazine in plasma was linear in the concentration range of 1–3000 ng mL^{-1} with correlation coefficient values >0.997 (the weight is $1/x^2$). Intra-day and inter-day coefficients of variance and accuracy were determined by measuring six replicates of QC samples at three concentration levels in human plasma. The mean extraction recoveries of ranolazine determined using three replicates of QC samples at three concentration levels in human plasma were found 89.4 ± 2.3%, 93.1 ± 4.6%, and 96.8 ± 5.8% for 5, 200 and 2400 ng mL^{-1}, respectively. These results all were summarized in Table 1, demonstrate that the coefficients of variance and accuracy values are within the acceptable range and the method is accurate and precise.

3.5. Matrix effects

In order to assess the possibility of a matrix effect caused by ionization competition between the analytes and co-eluents exists when using U-HPLC–MS/MS for analysis. Three different concentration levels of ranolazine (5, 200 and 2400 ng mL^{-1}) were evaluated by analyzing five samples at each level. Percent nominal concentrations estimated were within the acceptable limits (85.0–100.4%) after evaluating six different lots of plasma. The same evaluation was performed on I.S. (101.5%) and no significant peak area differences were observed. Thus, ion suppression or enhancement from plasma matrix was negligible for this method.

3.6. Stability

The stability of quality control plasma samples (5, 200 and 2400 ng mL^{-1}) were found stable in plasma when placed in the short term (8 h) room temperature, four freeze/thaw (−25 °C) cycles and stored at −75 °C for 2 months. In addition, the stability of ranolazine in processed quality control samples was also found

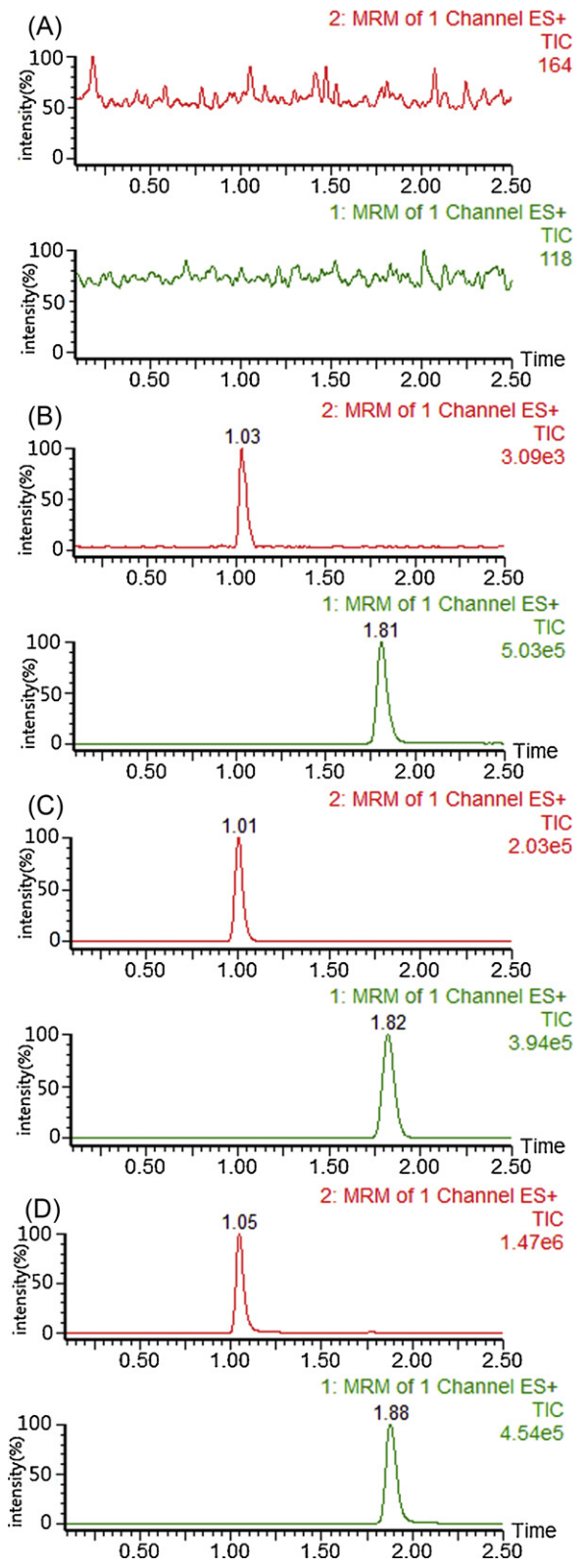

Fig. 3. Selective ion chromatograms (bottom-up order: Channel 1: I.S. m/z 342.4 → 115.9, collision energy 22 eV; Channel 2: ranolazine m/z 428.3 → 279.3 collision energy 24 eV). (A) Representative ion chromatograms of extracted blank human plasma sample. (B) Ion chromatograms of the LLOQ plasma spiked with 1 ng mL^{-1} of ranolazine. (C) Ion chromatograms of the plasma spiked with 100 ng mL^{-1} ranolazine and 25 ng mL^{-1} propafenone (I.S.). (D) Representative ion chromatograms of human plasma after 3.0 h after single-dose ranolazine 1000 mg oral administration.

Table 1
Extraction recovery, intra- and inter-day coefficients of variance of ranolazine in human plasma.

Concentration (ng mL^{-1})	Extraction recovery (n = 5)		Intra-day coefficients of variation (n = 5)			Inter-day coefficients of variation (n = 15)		
	Recoveries (%)	RSD (%)	Measured concentration (ng mL^{-1})	RSD (%)	Bias (%)	Measured concentration (ng mL^{-1})	RSD (%)	Bias (%)
1 (LLOQ)	88.5	10.1	1.1 ± 0.1	9.8	10.0	–	–	–
5	89.4	2.3	4.9 ± 0.4	8.6	2.2	5.1 ± 0.4	7.8	1.6
200	93.1	4.6	208.6 ± 10.0	4.8	4.3	213.5 ± 13.5	6.3	6.8
2400	96.8	5.8	2566.8 ± 66.7	2.6	7.0	2462.4 ± 169.9	6.9	2.6

Note: RSD, relative standard deviations and (–) no experimentation was performed.

Table 2
Stability data of ranolazine in human plasma under various conditions (n = 5).

Concentration (ng mL^{-1})	Room temperature (8 h)			−75 °C for 2 months			Freeze/thaw (4 cycles)			Autosampler (12 h)		
	Mean	RSD (%)	Bias (%)	Mean	RSD (%)	Bias (%)	Mean	RSD (%)	Bias (%)	Mean	RSD (%)	Bias (%)
5	4.4	5.1	−12.0	4.6	5.6	−8.0	4.7	7.7	−6.0	4.9	7.4	−2.0
200	195.7	7.1	−2.2	211.8	1.5	5.9	195.3	5.4	−2.3	178.4	4.2	−10.8
2400	2487	5.0	3.6	2411.7	1.6	0.5	2504.4	5.6	4.4	2223.0	4.4	−7.4

Note: RSD, relative standard deviations.

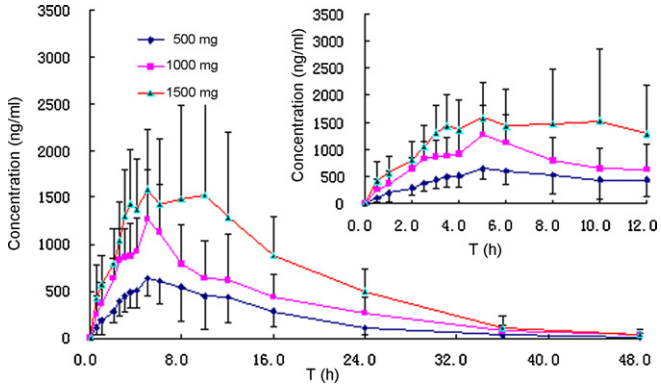

Fig. 4. Mean plasma concentration–time curve after a single oral dose of 500, 1000, or 1500 mg of ranolazine (n = 12, $\bar{x} \pm s$).

stable when placed in the autosampler at the ambient temperature (20 °C) for 12 h (Table 2).

3.7. Pharmacokinetic studies

The method was successfully applied to determine the plasma concentration of ranolazine up to 48 h after oral administration of 500, 1000 or 1500 mg ranolazine to the healthy volunteers. Mean plasma concentration–time profile is presented in Fig. 4. The pharmacokinetic parameters are listed in Table 3. The data in the single dose study show the linear relationship between AUC_{0-48} and the dose. There was no significant difference of T_{max} and $t_{1/2}$ among the three dosages, indicating the pharmacokinetic linearity of the three dosages within the studied dose range.

4. Discussion

To the best of our knowledge, this is the first study to characterize pharmacokinetic profile of ranolazine after administration of single doses in healthy Chinese subjects. Compared with previous pharmacokinetic research [15], The V/F in the present study ranged from 587.9(401.8) to 661.9(733.1) L, larger than that reported in white subjects (85–180 L). The plasma $t_{1/2}$ of ranolazine in all healthy Chinese subjects in the single-dose phase of the present study (6.5 [3.8] h) was longer than values reported in healthy white subjects (4.0–5.0 h); The reasons for the differences in $t_{1/2}$ and V/F between the present and previous studies of ranolazine are unclear, although variation in body weight may have played a role. However, because the previous studies were not conducted under the same conditions as in the present study, the existence of racial differences in ranolazine pharmacokinetics can be neither confirmed nor ruled out.

Interindividual variability in AUC and C_{max} values was considerable, with the CV ranging from 35.4% to 46.6% and 31.6% to 38.2%, respectively. Ranolazine is extensively metabolized in the liver by the cytochrome P450 (CYP) 3A and 2D6 enzymes [16], and is also known to be a substrate and moderate inhibitor of the P-gp efflux pump in the gastrointestinal tract, so this high variability may be due to the phenotype of isozymes CYP3A, P-gp and CYP2D6. Because of the P-gp may have significant effects on the bioavailability and first-pass metabolism of its substrates [16]. Therefore, inhibition of P-gp can lead to enhance the absorption of substrates and the potential for toxicity. Differences in the phenotype or activity of the metabolizing enzymes may result in altered effectiveness or increased incidences of adverse events in certain individuals. These suggest that monitoring of blood concentrations and individualized dosing are needed to ensure clinical

Table 3
Pharmacokinetic parameters of 12 healthy volunteers after oral administration of ranolazine (n = 12, $\bar{x}(s)$).

Parameter	Single dose		
	500 mg (n = 12)	1000 mg (n = 12)	1500 mg (n = 12)
AUC_{0-48}, ng mL^{-1} h^{-1}*	9071.9(3400.0)	16,573.5(6806.2)	29,324.5(10,857.2)
$AUC_{0-\infty}$, ng mL^{-1} h^{-1}*	9862.7(3152.0)	16,882.4(6790.8)	29,923.5(10,706.3)
C_{max}, ng mL^{-1}*	741.5(253.0)	1355.0(502.0)	2328.7(890.5)
T_{max}, h*	5.3(1.4)	4.2(1.2)	5.9(2.8)
$t_{1/2}$, h*	6.4(3.3)	6.4(3.5)	6.7(4.3)
CL/F, L/h*	60.9(30.2)	73.4(43.0)	58.1(25.8)
V/F, L*	587.9(401.8)	655.2(493.0)	661.9(733.1)

* No significant differences were found between the 3 dose groups. $p < 0.05$ was considered to be statistically significant.

therapeutic effectiveness and a favorable safety profile, although the pharmacokinetic-pharmacodynamic relationship needs to be clarified.

5. Conclusions

An U-HPLC–MS/MS assay for determination of ranolazine in human plasma was developed and validated with respect to sensitivity, accuracy, intra- and inter-day coefficients of variance and reproducibility, which in positive electrospray ionization mode using MRM and fit-for-purpose validated according to commonly accepted criteria [14]. The method has significant advantage over other techniques used for which provides the higher sensitivity using a simple protein precipitation procedure, which did not involve reconstitution or drying step to achieve the desired sensitivity, and a simple sample method of protein precipitation was used to extract the analyte and I.S. which provided excellent specificity and reproducibility, the run-time was only 2.0 min. This validated method is suitable for analysis of the large batches of samples and successfully used for different ranolazine dose pharmacokinetic studies.

In this group of healthy Chinese subjects, AUC and C_{max} increased proportionally with the dose, whereas $t_{1/2}$ was independent of the dose. The PK properties of ranolazine were linear after administration of single oral doses of 500–1500 mg. Furthermore, some of the main pharmacokinetic parameters of ranolazine may reflect racial differences.

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