Quantification of Rebamipide in Human Plasma by HPLC-MS/MS and Application to A Pharmacokinetic Study in Chinese Healthy Volunteers

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Abstract：

Background: Rebamipide was widely used for the treatment of gastric ulcer, gastritis, gastric mucosal lesions, but the large inter-individual variability in PK parameters was observed. The aim of this study was to investigate the pharmacokinetic of rebamipide in healthy Chinese volunteers, which is critical to the safety and efficacy.

Method: A selective and sensitive liquid chromatography–tandem mass spectrometry method was developed for the determination of rabamipide in human plasma. The separation was performed on Inertsil®ODS-3 column (150×4.6mm, 5μm), with a mobile phase constituted by methanol and 1% formic acid (70:30, V/V), with the flow-rate at 0.6ml/min. The detection was carried out on Agilent 6410 Triple Quadrupole mass spectrometer under positive-ion multiple reaction monitoring mode, and the respective mass transitions used for quantification of rebamipide and carbamazepine (internal standard, IS) were m/z 371.3→216.4 and m/z 237.2→194.2. The validated method was applied in the pharmacokinetic study of rebamipide in Chinese healthy volunteers under fasted condition.

Results: Calibration curves were linear over the concentration range of 5-400ng/ml. After single oral dose of 100 mg, the main pharmacokinetic parameters of rebamipide were as follows: C_{max} (165.11±50.53 ng/mL), AUC_{0-t} (637.30±208.67 ng·h/mL), T_{max} (2.71±1.18 h), $t_{1/2}$ (1.63±0.51 h). Double peak phenomenon was observed in mean plasma concentration curves.

Conclusion: The HPLC-MS/MS method developed in this article was proved to be of

great accuracy and precision, suitable for the rapid batch determination of rabamipide in pharmacokinetic and clinical studies. The pharmacokinetic of rabamipide in healthy Chinese volunteers was investigated according to this method, A secondary peak was observed in mean plasma concentration curves.

Keywords: Rebamipide, HPLC-MS/MS, Human plasma, Pharmacokinetic, Chinese healthy volunteers, Double peak

1. Intoduction

Rebamipide , (2-[4-(chlorobenzoylamino)]-3-[2(1H)-quinolinon-4-yl] propionic acid, is a quinolinone-derived gastroprotective agent, can increase the secretion of surface gastric mucus, enhance mucosal denfense, scavenge free radicals, inhibit pro-inflammatory cytokine secretion by immune cells and temporarily activate epidermal growth factor[1-6]. In 1990, rebamipide (Mucosta®1 tablets) was approved in Japan for gastric ulcer therapy. Now rebamipide is widely used in clinical practice for the treatment of gastric ulcer, gastritis, gastric mucosal lesions (erosion, haemorrhage, redness and oedema) in acute gastritis and acute exacerbations of chronic gastritis.

Rebamipide is a highly lipophilic compound, which is practically insoluble in ether and water and very slightly soluble in methanol and ethanol[7]. Because of its poor solubility and poor permeability via intestinal membranes, rebamipide is classified into Class IV compounds according to the US Food and Drug Administration Biopharmaceutics Classification System. According to previous studies[8], following a single oral administration of rabamipide 100 mg, the peak plasma level (220.57 ng/ml) was observed in 2.10 h and with a half-life of 1.93 h and the AUC was 903.46 ng/mL/h.

However, the inter-individual variability (IIV, 25–50%) in PK parameters was relatively large [9-10]. Therefore, study on the in vivo processes of rabamipide is critical to the safety, efficacy, also the development of generic medicines.

In this study, a more sensitive and rapid HPLC-MS/MS method was developed and validated; then the method was successfully applied to a pharmacokinetic study in 12 Chinese healthy volunteers after an oral dose of 100 mg rebamipide tablets.

2. Materials and Methods

2.1 Regents and materials

The rebamipide reference standard (purity: > 98 %) were purchased from TargetMol (Shanghai, China). Mucosta (100 mg of rebamipide, thin film coating, lot no. 6G97MT2) was produced by Otsuka, Zhejiang, China). Carbamazepine (internal standard, IS) was purchased from the National Institute of Food and Drug Control (purity 99.7%). Both of methanol and acetonitrile were HPLC grade from J.T.Baker. Pure water was obtained from Hangzhou Wahaha Group Co. Ltd. Formic acid was bought from Tianjin Kemiou Chemical Reagent Co., Ltd.

2.2 Instrumentation and Analytical Conditions

The HPLC-MS/MS procedures were performed using an Agilent series HPLC and an Agilent 6410 Triple Quadrupole mass spectrometer equipped with an electrospray ionization source. The separation of extracted plasma samples was performed on the Inertsil®ODS-3 column (150×4.6mm, 5μm). The mobile phase consisted of methanol –1% formic acid (70:30, V/V), the flow-rate was set at 0.6ml/min, and the injection volume was 10 ul.

Mass spectrometric analysis was performed in the ESI positive ion mode with the spray gas pressure at 350Pa. The protective air of nitrogen gas was 9.0L/min with the temperature (TEM) at 350℃. Quantification was performed by multiple reaction monitoring (MRM) of the protonated precursor ion and the related product ion for rabamipide using the internal standard method with peak area ratios and a weighting factor of $1/x^2$. The mass transitions used for rabamipide were m/z 371.3→216.4 and m/z 237.2→194.2 for IS. The specific parameters for rabamipide and IS were listed as follows: collision energy 13 eV and 20 eV, fragment electric voltage 135 eV and 100 eV, EMV 200V. All data were analyzed by Agilent 6410 Quantitative Analysis version analyst data processing software.

2.3 Preparation of calibration standards and quality control (QC) samples

The standard stock solutions of rabamipide (200μg/mL) for calibration standards and quality control were prepared by dissolving requisite amounts in methanol. Then diluted with methanol to get the working solutions for calibration (0.05, 0.1, 0.2, 0.5, 1.0, 2.0, 4.0 μg/ml) and quality-control (0.15, 0.8, 3.0 μg/ml). The stock solutions of IS (200μg/mL) were dissolved and diluted by methanol to get the working solution (800ng/mL). All the stock solutions and working solutions were stored at -20 °C. The calibration standards and QC samples were freshly prepared by spiking the respective working solutions with blank plasma. The concentration of calibration standards was 5.00, 10.0, 20.0, 40, 100, 200, 400 ng/mL, and QC samples were at concentration levels of 5.00 ng/mL (the lower limit of quantification QC, LLOQ), 15.0 ng/mL (low QC, LQC), 80 ng/mL (medium QC , MQC), 300 ng/mL (high QC, HQC).

2.4 Plasma sample preparation

An aliquot of 100μL plasma was spiked with 10μL internal standard solution, then a 300 μL aliquot of methanol was added. Then the sample were vortex mixed for 10min, and then centrifuged for 5 min at 10800 rpm. The supernatant was transferred and injected for LC–MS/MS analysis.

2.5 Method validation

This method was validated based on the guidance for Bioanalytical Method Validation Guideline published by the US Food and Drug Administration (2013), including selectivity, carryover, matrix effects, linearity, recovery, precision, accuracy and stability.

2.6 Subjects and Administration

The validated method was applied to a pharmacokinetic study of rabamipide in 12 healthy subject. The inclusion criteria included the following: healthy male or female subject between 18 and 50 years; body mass index ranging from 19 to 26kg/m^2; physical examination and laboratory tests were qualified; voluntarily sign a written informed consent prior to trial and full understanding of the content, process and possible adverse reactions. Subjects with any of the following criteria were excluded: allergies to rabamipide or its accessories; previous history of hypertension, hyperlipidemia or diabetes; blood donation or loss (>450mL) within 3 months; taking research drugs or participating in other clinical trials within 3 months; had a history of alcohol abuse in the last 2 years or drug abuse; intake of any prescription or nonprescription drug, food supplements, or herbal medicines within 14 days of the first dosing day of the study. The

study was conformed to the Declaration of Helsinki. The protocol, patient information, and consent form were reviewed and approved by the Ethics Committee of the Qilu Hospital Affiliated to Shandong University. The written informed consent was given to each study subject before the screening. All the subjects were fasted for at least 10 hours before drug administration, then each subjects received 1 table of rabamipide (100mg, lot: 6G97MT2) with 240ml water on the first day. No water was allowed 1h before and after the administration. The standard meals were provided at 4 h and 10 h after administration for all the subjects. Blood samples(4ml) were collected using heparin vacuum blood collection tube at pre-dose and 0.25h, 0.5 h, 0.75h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h, 5h, 6 h, 8h and 12 h after administration. The blood were centrifuged immediately at 3000rpm for 10min at 4℃ and stored at -20 °C until analysis.

3. Results

3.1 Method validation

3.1.1 Selectivity

Six blank human blood sample from different people were used to investigate the potential interference of endogenous plasma components with rabamipide and IS. After the extraction procedure and chromatographed, the MRM chromatograms of blank plasma were compared with the LLOQ (5 ng/mL) and a plasma sample from a healthy volunteer (Fig 1). The retention time of rabamipide and IS were 6.76 and 6.05 min. No distinguishable interferences from endogenous substances were found around the retention times of rabamipide and IS.

3.1.2 Carryover

Carryover effect was conducted by immediately injecting blank plasma samples after consecutive injection of Upper Limit of Quantification (ULOQ) samples. The response of rabamipide in blank plasma samples should be within 20.0% of that in LLOQ sample and be within 5.0% for the IS. No significant carryover peaks were observed at the retention time of rabamipide and IS. This indicated that the result of sample which injected after high concentration samples is reliable.

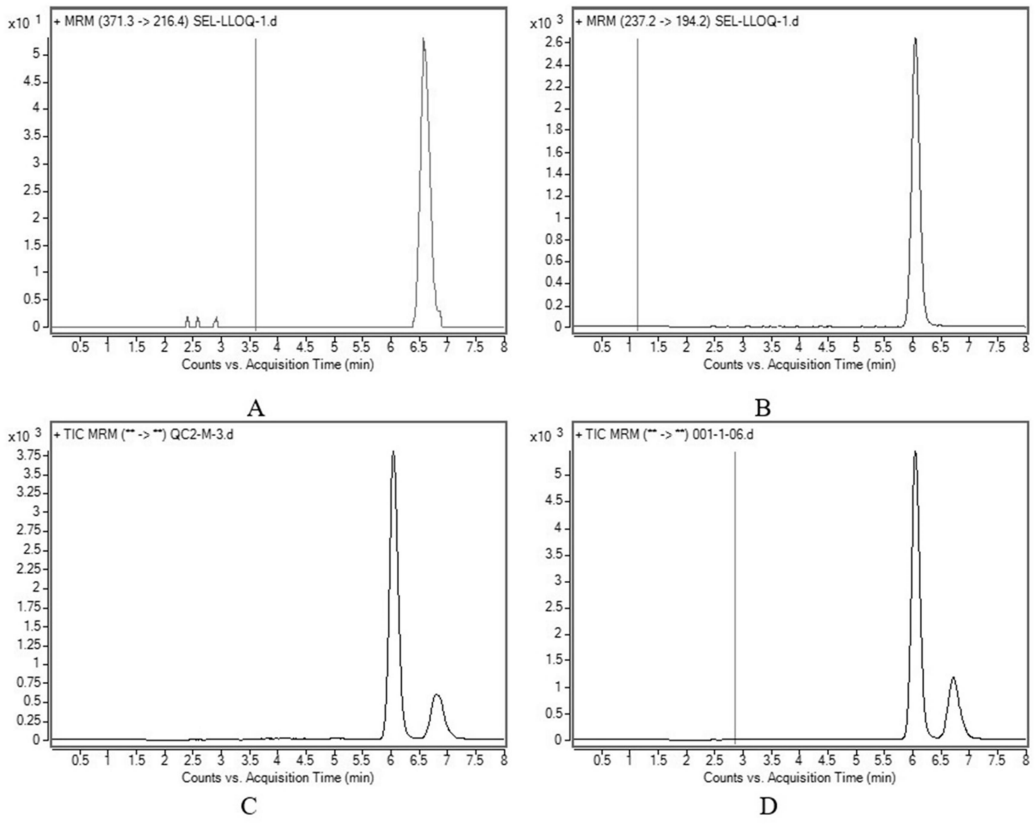

Fig 1 Typical chromatograms of standard solution of rabamipide (A) and IS (B), blank plasma spiked with rabamipide and IS (C), and plasma sample of subject NO.1 after 1.5h of oral administration (D).

3.1.3 Calibration Curve and LLOQ

The calibration curve of rabamipide in human plasma was established from 5-400ng/ml, including a double blank sample (a plasma sample processed without IS), a blank sample (a plasma processed with IS), and seven concentrations of rabamipide

including the LLOQ (5.00, 10.0, 20.0, 50, 100, 200, 400 ng/mL). Using a quadratic equation with a weighting factor of $1/x^2$, the correlation coefficient (r^2) were more than 0.99, each calculated standard concentration was not more than 15% deviation from the nominal value, except for the LLOQ which was set at 20%. The typical calibration curve was y = 0.0036 x + 0.0008 (R^2=0.9966), where Y represents the peak area ratio of rabamipide and IS, and X represents the concentration of rabamipide. The signal-to-noise ratio of LLOQ was more than five.

3.1.4 Recovery

The extraction recovery was determined by comparing chromatographic peak areas of extracted QC samples to that from post-extraction blank plasma spiked with rabamipide and IS at corresponding concentrations. Six replicates at two concentration level (QC-L, QC-H) were applied. The extraction recoveries of rabamipide were 97.70±0.78 and 95.64±5.11 at two QC levels, IS was 97.88±3.87. All the RSD were within ± 15%. This data proved that the protein precipitation procedure was sufficient and was not concentration-dependent.

3.1.5 Matrix effect

Matrix effect was analyzed by calculating the ratio of peak areas of the post-extraction spiked with rabamipide and IS to those of the rabamipide resolved in mobile phase at corresponding concentrations. The coefficient of variation (CV) of IS-normalized matrix factors, which means the ratio of the matrix factor of rabamipide to that of the IS, were supposed within ± 15%. The results were shown in table 1, the RSD of IS-normalized matrix factors for each QC level were less than 5.85%,

suggesting that there was no significant matrix effect.

Table 1 Recovery and matrix effect data of rabamipide in human plasma (n = 6).

Concentration (ng/ml)	Recovery			IS-normalized matrix factor		
	Mean(%)	SD(%)	RSD(%)	Mean (%)	SD(%)	RSD(%)
15	94.70	0.78	0.83	105.72	6.18	5.85
300	95.64	5.11	5.34	98.05	1.98	2.01
IS	97.88	3.87	3.96			

3.1.6 Accuracy and precision

The Intra-day and inter-day accuracy and precision were estimated by analyzing four concentration levels (LLOQ, QC-L, QC-M, QC-H) samples in six replicates on three analysis batches performed in three consecutive days. The precision was determined by relative error (RE %) which was required to be within ± 15% of nominal concentration (± 20% for LLOQ). The intra-day and inter-day precision was expressed as the relative standard deviation (RSD %) with the acceptance criteria within ± 15% for three QC sample and ± 20% for LLOQ. The results were summarized in Table 2. The intra-day and inter-day precision was between 0.6% and 5.1% and the RE% of intra-day and inter-day were ranged from -6.4% to -0.1%, with in the accepted variable limits.

Table 2 Intra-day and inter-day precision and accuracy for the quantification of rabamipide in human plasma (n=6).

QC level	Intra-day			Inter-day		
	Mean conc. (ng/mL)	RSD (%)	RE (%)	Mean conc. (ng/mL)	RSD (%)	RE (%)

LLOQ	4.99	2.51	-0.3	4.80	5.1	-4.1
LQC	14.98	1.9	-0.1	14.46	4.8	-3.6
MQC	74.85	0.9	-6.4	76.64	4.6	-4.2
HQC	291.48	0.6	-2.8	294.49	3.8	-1.8

3.1.7 Dilution accuracy

The Dilution Quality Control (DQC) was set at 600 ng/mL and diluted by 2-fold with blank plasma to the high QC level in five replicates. The diluted samples were analyzed with the accuracy and precision calculated and compared to high QC samples. The accuracy (RE%) and precision (RSD%) were 102.8% and 2.0%, which can meet the requirements of ± 15.0% for RE% and less than 15.0% for RSD%.

3.1.8 Sample Stability

The stability of rabamipide in plasma was investigated by analyzing QC samples at low and high concentration levels on three replicates at the following conditions: room temperature for 3 hours, freeze at −20 ℃ for 1, 3 and 19 days, three freeze-thaw cycles at −20 ℃, in autosampler at 4 ℃ for 23 h. Table 3 shows that the rabamipide was stable in plasma under the indicated conditions, with the precision less than ± 15%.

Table 3 Stability of rabamipide in human plasma (n = 3).

Storage conditions	Nominal conc. (ng/mL)	Measured conc. (ng/ml, Mean±sd)	RSD (%)	RE (%)
Room temperature stability (25 ℃, 3h)	15.05	14.92±0.77	5.16	-0.55
	301.06	301.87±16.52	5.47	0.62
Autosampler stability	15.05	15.56±0.30	1.92	3.72

(4 °C, 23h)	301.06	321.57±28.64	8.91	7.19
Long-term stability	15.05	14.68±0.32	2.15	-2.12
(-20 °C, 19d)	301.06	286.04±5.41	1.89	-4.65
Freeze-thaw stability	15.05	13.53±0.10	0.75	-9.77
(-20 °C, three cycles)	301.06	292.16±3.22	1.10	-2.61

3.2 Pharmacokinetic of rabamipide in Chinese healthy volunteers

The validated analytical method was successfully applied to analysis the plasma concentration of rabamipide for the PK study. 12 volunteers were include into this study, no serious adverse events occurred and no laboratory adverse experiences were reported during the entire trial. The significant pharmacokinetic parameters including C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $t_{1/2}$, λz were calculated by DAS (version 2.1.1) according to non-compartment mode. The mean plasma concentration-time profile of rabamipide in Chinese healthy volunteers after single oral administration of 100 mg tablet in fasted condition were displayed in Fig2. And the corresponding pharmacokinetic parameters were listed in Table 4.

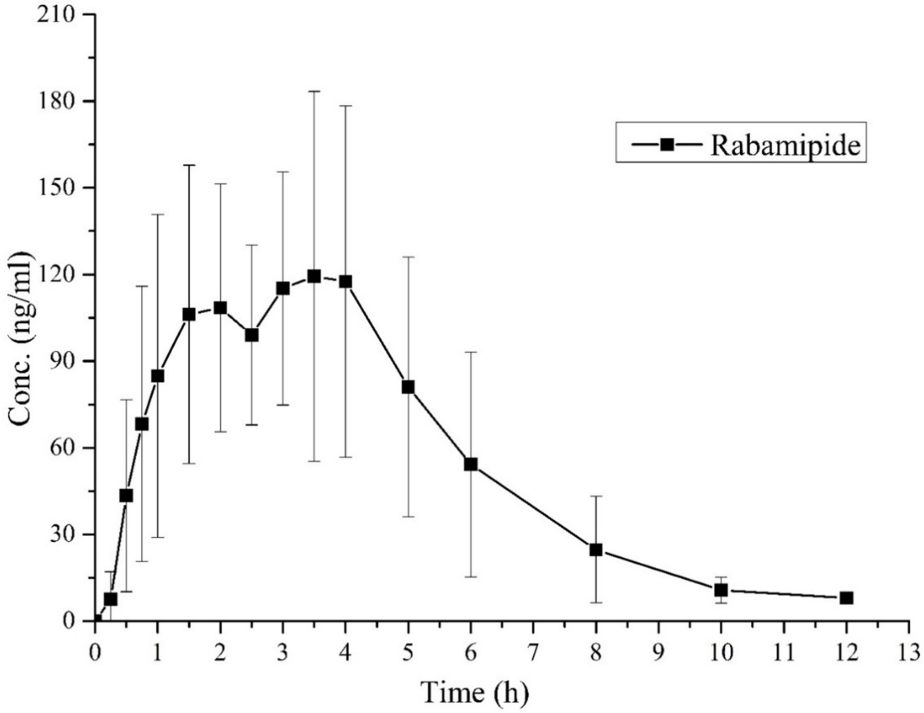

Fig 2 Mean plasma concentration-time curve of rabamipide after oral administration of 100mg (n=12)

After oral administration of 100mg rabamipide in the fasted condition, the peak concentration (165.11±50.53 ng/mL) of rabamipide was observed at approximately 3 h after administration. AUC_{0-t} was 637.30±208.67 ng·h/mL and the half-life was 1.63±0.51 h. Double peak was observed in mean plasma concentration curves of rabamipide.

Table 4 Pharmacokinetic parameters of rabamipide measured in Chinese healthy volunteers (n=12).

Parameters	Mean ± SD
C_{max} (ng/ml)	165.11±50.53
AUC_{0-t} (ng·h/ml)	637.30±208.67
$AUC_{0-\infty}$ (ng·h/ml)	665.16±206.30

T_{max} (h)[a]	2.71±1.18
$T_{1/2}$ (h)	1.63±0.51

4. Discussion

A high sensitive and rapid HPLC-MS/MS method was developed and adequately validated for the quantification of rebamipide in human plasma. In previous studies for the determination of rebamipide in biological fluids, multiple steps for the extraction like solid-phase extraction made the method complicated and time-consuming [8, 10-11]. In this study, a simple protein precipitation procedure and a more sensitive lower limit of quantification (LLOQ), make this method more rapid and convenient and suitable for the analysis of large numbers of plasma samples obtained from clinical studies.

Then the validated method was successfully used to investigate the pharmacokinetics of rebamipide in Chinese healthy volunteers following 100 mg single oral doses at fasted condition. After an oral administration of 100mg rabamipide tablet, the main pharmacokinetic parameters were as follow: C_{max} (165.11±50.53 ng/mL), AUC_{0-t} (637.30±208.67 ng·h/ml), $T_{1/2}$ (1.63±0.51 h). The C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and $T_{1/2}$ in Chinese healthy volunteers were significantly lower than that of Korean volunteers reported by Cho et al[8]. A secondary peak was observed after the peak concentration in plasma concentration–time curve. Because of its poor solubility and poor permeability via intestinal membranes[12], rebamipide has large inter-individual variability (IIV, 25–50%) in PK parameters. The double-peak phenomenon is a typical example indicating the complex kinetics of drug absorption after oral dosing. Possible reasons including the interaction between drugs and bile salts in the intestinal lumen; the

enterohepatic circulation; the two different sites of drug absorption; the irregular pattern of gastric emptying[13-15]. The secondary peaks or a concentration plateau of rabamipide was observed in several published studies, but the authors did not describe this phenomenon[15-17]. The population pharmacokinetic analysis of rabamipide suggests that the efflux transporter MDR1 3435C>T allele affects the substantial inter-individual variability in the absorption according to genetic polymorphism[18]. However, there is no conclusion about these phenomena. In the future pharmacokinetic study or bioequivalence study of rabamipide, the double-peak must be taken into account.

5. Conclusion

The present HPLC-MS/MS method was fully validated according to FDA guidelines, with liner range between (5-400ng/ml), the method was proved to be of great accuracy and precision, suitable for the rapid batch determination of rabamipide in pharmacokinetic and clinical studies. Sample preparation was achieved by protein precipitation with methanol. By using this method, the pharmacokinetic study of rabamipide was carried out in healthy Chinese volunteers. After single oral administration of 100 mg rabamipide, the main pharmacokinetic parameters were as follow: C_{max} (165.11±50.53 ng/mL), AUC_{0-t} (637.30±208.67 ng·h/ml), $T_{1/2}$ (1.63±0.51 h). Moreover, double peak phenomenon was observed in mean plasma concentration curves.

Conflict of interest

The authors have declared no conflict of interest.

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