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Article

Pharmacokinetics and safety of repirinast tablets in healthy Chinese subjects

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Repirinast is a new, synthetic, disodium cromoglycate-like antiallergic agent for oral administration in humans. This study evaluated the safety, tolerability and pharmacokinetics of repirinast tablets in healthy Chinese volunteers. This was a phase I, open-label, randomized, single- and multiple-dose study. Subjects were assigned to receive a single dose of repirinast tablet at either 150, 300, or 450 mg, or multiple doses of 150 mg twice daily for 5 days. Plasma samples were analyzed with LC-MS/MS. Pharmacokinetic parameters of active metabolite MY-1250 (deesterified repirinast) were calculated using non-compartmental analysis with WinNonlin software. Statistical analysis was performed using SPSS software. All adverse events (AEs) were mild and of limited duration. No serious adverse event (SAE), death or withdrawal from the study was observed. In the single-dose study, C_{max} was reached at about 0.75 hour, and the mean $t_{1/2}$ was approximately 16.21 hours. Area under curve (AUC) and C_{max} increased with dose escalation, but dose proportionality was not observed over the range of 150 to 450 mg. In the multiple-dose study, the steady-state was reached within 3 days with no accumulation. Repirinast tablet was well tolerated in healthy Chinese subjects.

Keywords: Repirinast/safety/pharmacokinetics. Single dose. Multiple dose. China.

INTRODUCTION

Repirinast is a new, synthetic, disodium cromoglycate-like, antiallergic agent for oral administration in humans and has been marketed in Japan since 1987 for the treatment of asthma. (Miyamoto *et al.*, 1986; Takahashi *et al.*, 1986; Takishima *et al.*, 1986). Repirinast, as a prodrug, is immediately hydrolyzed to the active metabolite MY-1250 (deesterified repirinast) after oral administration. The metabolite MY-1250 is pharmacodynamically active as it prevents the IgE-mediated allergic response by inhibiting the release of mediators triggered by antigen-antibody complexes (Yamada *et al.*, 1988). Marketed as Romet®, repirinast was first developed by Mitsubishi Chemical Corporation in Japan. It was reported that repirinast was absorbed rapidly and hydrolyzed to active metabolite MY-1250 after administration of a single 150 mg dose with the C_{max} attained within approximately 2 hours. In urine, 20.25% metabolite was MY-1250 and 2.7% was other active metabolite within 24 hours of oral administration. No accumulation appeared upon repeated doses.

An oral formulation of repirinast (150 mg tablets) was developed in China. Although the pharmacokinetics of repirinast in Japanese and Caucasian subjects has been reported (Iwamoto *et al.*, 1986; Takagi *et al.*, 1989; Asamoto *et al.*, 1989; Beermann *et al.*, 1992), no pharmacokinetic data of repirinast in Chinese subjects is available. In this paper, the pharmacokinetics, safety and tolerability of repirinast tablets after single and multiple doses in healthy Chinese subjects are reported for the first time. The study was performed at the Second Affiliated Hospital of Soochow University (Suzhou, China) in 2015.

MATERIAL AND METHOD

Drug and reagents

Three doses (150 mg, 300 mg and 450 mg) of repirinast tablets (Batch: 201307012, Specifications: 150 mg/tablet) for single and multiple doses were made. Repirinast (Batch: 20130601D, purity:

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99.8%) and MY-1250 reference substance (Batch: 20140501D, purity: 99.3%) were obtained from Shanghai Cares Biotechnology Co., Ltd. (Shanghai, China). Levetiracetam reference substance (internal standard, IS, Batch: 201308-2, purity: 99.8%) was obtained from Zhejiang Huahai Pharmaceutical Co., Ltd (Linhai, China). HPLC-grade methanol was purchased from Merck KGaA Company (Darmstadt, Germany). Analytical grade ammonium acetate and ammonia hydroxide were purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). Analytical grade hydrochloric acid was purchased from Shanghai Lingfeng Chemical Reagent Co., Ltd. (Shanghai, China). Distilled water was produced by a Milli-Q water purification system (Millipore, Bedford, USA).

Instruments

HPLC was performed using a 1200 Series device (Agilent Technologies, Palo Alto, CA, USA). Mass-spectrometric detection was performed on an API 4000 triple-quadrupole instrument (ABI-SCIEX, Ontario, Canada).

Subjects

Healthy Chinese volunteers, aged 19-45, with a body mass index (BMI) of 19-24 kg/m^2 and a body weight of more than 50 kg were eligible for inclusion in the study. Subjects were ascertained to be healthy through medical interview, physical examination, checking of vital signs, clinical laboratory tests (e.g. haematology, blood chemistry and urinalysis) and a 12-lead ECG test within 2 weeks before the first dosing of the study medication. Female subjects had to be using double barrier contraception or surgically sterilized.

Persons were excluded from the study if they were: infected with hepatitis B or C virus or HIV or Syphilis; pregnant or breastfeeding; had a history of pulmonary, cardiovascular, neurological, psychiatric, endocrine or coagulation disorders; had renal or hepatic disease or any physical attributes that may influence the trial results; were medicated or using drugs of any kind in the two week period before the start of the study; had a history of abusing drugs or alcohol; had a history of smoking more than five cigarettes per day or equivalent; had participated in another drug study or donated blood in the three month period prior to this study.

The study was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (GCP) in China. The study protocol was reviewed and approved by the Independent Ethics Committee of the Second Affiliated Hospital of Soochow University (approval numbers: 2013/35). All subjects provided written informed consent prior to entering the study.

Study design

This was a phase I, open-label, randomized, single and multiple-dose study. Twenty subjects were randomized to group 1 or group 2 (5 females and 5 males in each group). The subjects were hospitalized at 8:00 pm the night before dosing and required to fast overnight (10 h). Throughout the sequential single-dose and multiple-dose trials, repirinast tablets were administrated in the fasting state. After the trial, the subjects were released and visited the clinic for a test of vital signs, 12-lead ECG, physical examination, and other routine laboratory tests. Additional laboratory tests were ordered by the principle investigator.

Single dose administration

The single dose of repirinast tablet was 150 mg, 300 mg or 450 mg once daily. On day 1 and day 8, subjects in group 1 were randomly assigned to receive a single oral administration of either 300 mg or 450 mg repirinast tablets. Subjects in group 2 received a single oral administration of 150 mg repirinast tablet on day 1. In the single dose study, subjects were required to fast overnight (10 h) before dosing. Water intake was prohibited within the 2 h following drug administration and a standard lunch was served 4 h after dosing. Blood samples (3 mL each) were collected in heparinized vacutainers pre-dose (0 h) and 10 min, 20 min, 0.5 h, 0.75 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h, 36 h, and 48 h after dosing. During the study, blood samples were separated by centrifugation at 3200 × g at 4 °C for 10 min. All plasma samples were stored at -30 °C until analysis.

Multiple dose administration

After the single-dose phase from day 1 to 3, subjects from group 2 were assigned to receive 150 mg of repirinast tablet every 12 h from day 3 to day 7. Subjects were required to fast overnight (10 h) before the first (day 1) and last (day 8) dosing, and to fast 1 hour every 12 h before dosing from day 3 to day 7. On days 6, 7, and 8, predose blood samples (3 mL each) were collected prior to the morning dose to evaluate the achievement of steady state condition. On day 8, blood samples were collected predose (0 h) and at the same time points as in the single-dose study to 48 h after dosing. All the other experimental conditions were in consistent with those in the single dose phase.

All of the subjects were hospitalized in the phase I unit ward of the Second Affiliated Hospital of Soochow University during the study. The subjects were required to refrain from smoking, alcohol and caffeinated beverages. Strenuous exercise was not allowed on each dosing day. Medications (including vitamins, herbal supplements and traditional Chinese medicines) were not permitted.

Analytical methods

Plasma concentrations of MY-1250 (the active metabolite of repirinast) were determined using the liquid chromatography-tandem mass spectrometry (LC-MS/MS) method developed in our lab (Huang *et al.*, 2017). This analytical method for analyzing the plasma consists of the following steps: 204 µL of pretreated plasma, 50 µL of 400 ng/mL I.S. (levetiracetam) working solution and 600 µL of methanol were vortexed in a 1.5 mL polypropylene tube for 1 min and centrifuged at 21,130 × *g* at 4 °C for 5 min. 400 µL of the supernatant was mixed with 800 µL of water, and 50 µL mixture was injected into the LC-MS/MS system (API 4000, Applied Biosystem Sciex, Ontario, Canada). The analyte was separated on a C18 column (ZORBAX Eclipse plus C18, 4.6 mm × 100 mm, 3.5 µm) equipped with a Phenomenex C18 Security guard column and the analytical column was maintained at 35 °C. Mobile phases were 6 mM ammonium acetate (0.02% ammonia hydroxide included) (A) and methanol (B). The following gradient conditions were used for a 50 µL sample injection and constant 800 µL/min flow rate: 0-8.5 min A: B (75:25); 8.6-9.6 min A: B (5:95); 9.7-13 min A: B (75:25). Mobile phases were controlled into the mass spectrometry system between 2.0 - 10.5 min. The MS/MS was carried out in the positive ionization mode with MY-1250 and I.S. being identified by the multiple reactions monitoring (MRM) at m/z 286.1→198.2 and m/z 171.3→126.2, respectively. The calibration curves were linear over the range of 2 ~ 1500 ng/mL for MY-1250. The LLOQ was 2 ng/mL. The intra- and inter-assay precisions were less than 15%. The result of extraction recoveries for MY-1250 ranged from 87.0% to 88.1%. The result of matrix effect for MY-1250 ranged from 99.2% to 100.2%. The stock solution was stable for 24 h at ambient temperature and for at least 26 days at 2~8 °C. The plasma samples were stable for 6 h at ambient temperature, during the three freeze-thaw cycles and for at least 65 days at -30 °C. The post-preparative solution was stable for 6 h at ambient temperature and for 40 h in the autosampler at 4 °C. Low-, medium-, and high-quality control samples (4, 80, 1200 ng/mL) were analyzed with the study samples to ensure the quality of analysis.

Safety and tolerability evaluation

Adverse events (AEs), physical examinations, clinical laboratory tests, 12-lead ECGs and vital signs were monitored for safety and tolerability assessment. The relationship of AEs to the study drugs were graded as not related, probably not related, possibly related, probably related or definitely related by the investigators. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Pharmacokinetic and statistical analysis

Pharmacokinetic analysis was performed with WinNonlin software (Version 6.3, Pharsight Corporation, Mountain View, CA, USA), utilizing non-compartmental analysis. The maximum plasma concentration (C_{max}) and time to C_{max} (t_{max}) were directly obtained from the concentration-time curves. The terminal-phase elimination half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$, where λ_z was the slope of the apparent elimination phase of the natural logarithmic (ln) transformation of the plasma concentration-time curve, which was estimated using liner regression. The area under the plasma concentration-time curve from time zero to t (AUC_{0-t}), where t is the time of last measurable sample, was calculated according to the linear trapezoidal rule. The AUC from time zero to infinity ($AUC_{0-\infty}$) was estimated as $AUC_{0-t}+C_t/\lambda_z$, where C_t was the plasma concentration of the last measurable sample. Apparent total clearance (Cl/F) was calculated as Dose/$AUC_{0-\infty}$ or Dose/AUC_{ss} and apparent total volume of distribution (V_z/F) was calculated as CL/λ_z. Attainment of steady state by day 8 was evaluated by regressing the natural logarithmic (ln) transformation of trough concentrations on day 6, 7 and 8 over time. The steady state was attained if the slope was not statistically different from zero. The steady state AUCs (AUC_{ss}) over the dosing interval (τ=12 h) and C_{avg} ($AUC_{ss}/_{\tau}$) were calculated. The degree of fluctuation (DF) was calculated as $(C_{max}–C_{min})/C_{avg}$. Accumulation ratios were defined as the steady-state $AUC_{0-\tau}$ to the single-dose $AUC_{0-\tau}$ ratio or the steady state C_{max} to the single dose C_{max} ratio, namely, $R_{AUC} = AUC_{0-\tau}$ (steady state)/$AUC_{0-\tau}$ (single-dose) (τ=12 h) and $R_{Cmax}=C_{max}$ (steady state)/C_{max} (single dose), respectively.

Statistical analysis was performed using SPSS software (version 17.0, SPSS, Inc, Chicago, IL, USA). The results are expressed as the mean ± SD. Prior to the analysis, dose-dependent parameters (C_{max} and AUC) were determined using natural logarithms of individual values. For the exploration of dose proportionality, the

slope β and 90% confidence intervals (CIs) obtained from the power model as ln(AUC or C_{max}) = α + β × ln (dose) were computed by covariance (ANOVA). The regression coefficient was significant at level 0.1. The pre-defined criterion was set as (0.80, 1.25) and (0.75, 1.33) for AUC and C_{max}, respectively. The criterion interval resulted in the value of (0.80, 1.20) and (0.74, 1.26) for AUC and C_{max}, respectively. The differences in pharmacokinetic parameters among dose groups were compared using the analysis of *t*-test, with the exception of t_{max}, for which the non-parametric test (NPT) was used. Statistical comparisons between pharmacokinetic parameters of single and multiple doses were performed by the paired *t*-test. The differences in C_{min} on day 6, 7, and 8 were compared using ANOVA to determine whether the steady state was reached in the multiple dose study.

RESULTS

Subjects

A total of 20 healthy subjects (10 males and 10 females) were enrolled in the study. The randomization scheme of subjects is shown in Table I. No subject dropped out during the study. There were no significant differences among the 20 subjects with regard to age, height, weight, or body mass index (Table II).

Pharmacokinetic assessment

Single-dose pharmacokinetics

The mean plasma concentration-time curves after oral administration of 150, 300, or 450 mg repirinast tablets are shown in Figure 1, the pharmacokinetic parameters are presented in Table III. The results indicate that repirinast was absorbed rapidly, with a median t_{max} 0.75 h of active metabolite MY-1250 across all of the dose cohorts. After reaching peak exposure, the plasma disposition of MY-1250 had a mean $t_{1/2}$ of 16.21 h, which was independent of dose. The mean oral apparent total plasma clearance (Cl/F) and Vz/F of MY-1250 were 164.4 L/h and 3296 L, 202.2 L/h and 4555 L, and 237.5 L/h and 5269 L for the 150, 300, and 450 mg dose cohorts, respectively. Over the dose range of 150 to 450 mg, the mean C_{max} increased from 308.9 to 441.7 ng/mL, the AUC_{0-t} increased from 937.0 to 1955 h·ng/mL and the $AUC_{0-\infty}$ increased from 1032 to 2272 h·ng/mL. The criterion intervals were (0.74, 1.26) for C_{max} and (0.80, 1.20) for AUC. However, the mean slopes (90% CIs) were 0.373 (0.075, 0.672) for C_{max}, 0.665 (0.397, 0.933) for AUC_{0-t}, and 0.679 (0.404, 0.955) for $AUC_{0-\infty}$. The 90% CIs for the ratio of dose-normalized of C_{max} and AUC indicated that there was no apparent dose-proportional relationship over the range of 150 to 450 mg. The t_{max} and $t_{1/2}$ were dose-independent (P>0.05).

TABLE I - The randomization scheme of subjects

Subject	day1	day2	day 3 - day 7	day8
group 1 (N=10)	single-dose 300 mg or 450 mg	-	-	single-dose 300 mg or 450 mg
group 2 (N=10)	single-dose 150 mg	-	multiple-dose 150 mg twice daily	single-dose 150 mg

TABLE II - Subject demographics, mean ± SD (range)

Characteristic	Single-dose	Single-dose & Multiple-dose
	300 mg & 450 mg	150 mg
n	10	10
Gender		
male	5	5
female	5	5
Age (y)	23 ± 2 (21-27)	26 ± 2 (22-28)
Bodyweight (kg)	56.7 ± 4.6 (50.0-64.0)	58.1 ± 7.5 (51.0-76.0)
Height (cm)	164.2 ± 5.8 (158.0-177.0)	165.8 ± 7.6 (154.0-179.0)
BMI (kg/m^2)	21.0 ± 1.7 (19.2-23.4)	21.1 ± 1.3 (19.5-23.7)

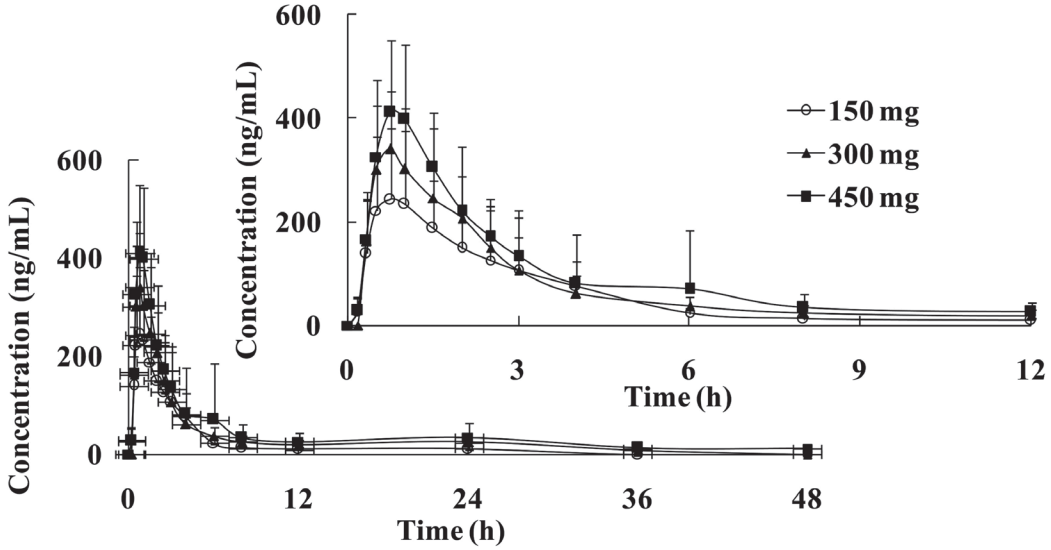

FIGURE 1 - Mean plasma concentration-time curves of MY-1250 in healthy Chinese subjects after a single oral administration of repirinast tablet 150, 300 or 450 mg (mean ± SD).

TABLE III - Main pharmacokinetic parameters of MY-1250 after a single oral dose of repirinast tablet (mean ± SD)

Parameter	150 mg (n=10)	300 mg (n=10)	450 mg (n=10)
C_{max} (ng/mL)	308.9 ±141.8	363.6 ±149.2	441.7 ± 139.6
t_{max} (h)	0.75 (0.50-3.00)	0.75 (0.50-1.50)	1.00 (0.50-1.50)
AUC_{0-t} (h·ng/mL)	937.0 ± 330.8	1492 ± 534	1955 ± 902
$AUC_{0-\infty}$ (h·ng/mL)	1032 ± 310.1	1720 ± 632	2272 ± 1212
$t_{1/2}$ (h)	13.83 ± 7.51	17.27 ± 11.72	17.54 ± 14.67
Cl/F (L/h)	164.4 ± 75.9	202.2 ± 94.8	237.5 ± 91.6
Vz/F (L)	3296 ± 2144	4555 ± 2670	5269 ± 3407

Multiple -dose pharmacokinetics

The mean plasma concentration-time curves of MY-1250 following multiple dose administration of 150 mg repirinast tablets are presented in Figure 2, the pharmacokinetic parameters are presented in Table IV. Attainment of steady state was achieved by day 6 because, per our analysis plan, the regression slope of the natural logarithmic (ln) transformation of trough concentrations on day 6, 7, and 8 over time was not statistically different from zero. The mean steady-state $t_{1/2}$ was 13.83 ± 5.26 h, which is comparable to the $t_{1/2}$ of a single dose (13.83 ± 7.51 h). The accumulation index was 1.078 (90% CI, 0.833~1.324) based on the AUC_{0-t}, and 0.849 (90% CI, 0.545~1.152) based on C_{max}, indicating that there was no further accumulation of repirinast after multiple administrations. The Cl/F, Vz/F, t_{max} and $t_{1/2}$ showed no significant difference between the first and the last dose.

Safety and tolerability assessment

The only adverse event observed during the course of this study was elevated alanine aminotransferase (1/20, 5%), which was observed in one subject after administration of 150 mg repirinast tablets every 12 h for 5 days. This is a known adverse reaction to repirinast and was likely related to the investigational drug.

The reported AE was mild or moderate in intensity and there were no SAEs, deaths or withdrawals. The subject recovered without medication or other treatment. There were no abnormal vital signs after treatment with repirinast tablets. When compared to baseline values acquired in the screening period, there were no clinically significant changes in the ECG data. Therefore, repirinast tablet was shown to be safe and well tolerated in healthy Chinese subjects.

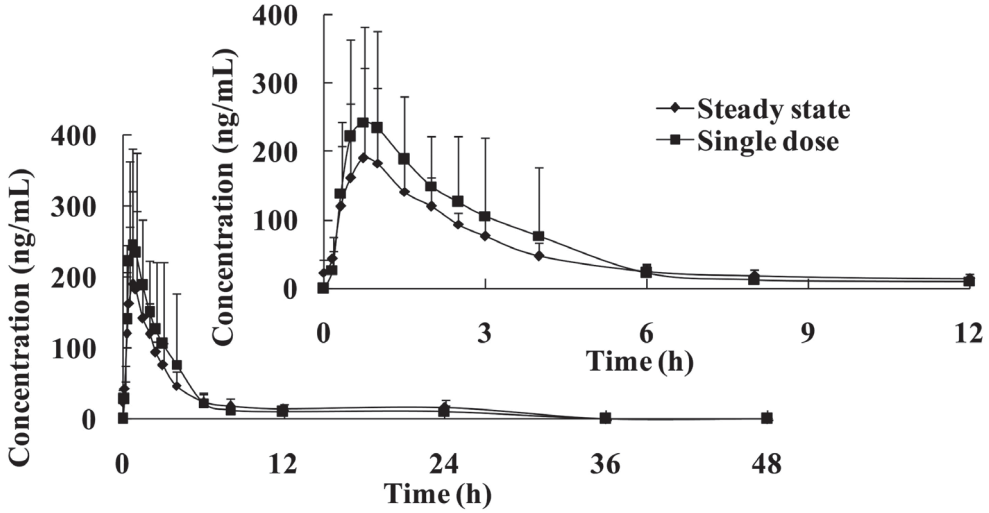

FIGURE 2 - Mean plasma concentration-time curves of MY-1250 in healthy Chinese subjects following multiple doses of 150 mg repirinast tablet every 12 h for 5 days (mean ± SD).

TABLE IV - Main pharmacokinetic parameters of MY-1250 in healthy Chinese subjects following multiple doses of 150 mg repirinast tablet every 12 h for 5 days (mean ± SD)

Parameter	single dose (d1)	multiple dose (d8)
C_{max} (ng/mL)	308.9 ± 141.8	216.0 ± 119.3
t_{max} (h)	0.75 (0.50-3.00)	0.75 (0.50-2.50)
AUC_{0-t} (h·ng/mL)	937.0 ± 330.8	929.7 ± 344.5
$AUC_{0-\infty}$ (h·ng/mL)	1032 ± 310	1021 ± 365
$t_{1/2}$ (h)	13.83 ± 7.51	13.83 ± 5.26
Vz/F (L)	3296 ± 2144	3160 ± 1558
Cl/F (L/h)	164.4 ± 75.9	170.6 ± 75.7
C_{avg} (ng/mL)	-	51.51±13.49
AUC_{SS} (h·ng/mL)	-	618.1 ± 161.9
DF	-	362.9 ± 139.0
R_{cmax}	-	0.849 ± 0.523
R_{AUC}	-	1.078 ± 0.424

t_{max} is shown as median (range); DF, degree of fluctuation.

DISCUSSION

In this study, the pharmacokinetics and safety of repirinast tablets in healthy Chinese volunteers is reported for the first time. This study was divided into two parts: single and multiple dose studies.

In the single dose study, C_{max} and AUC increased with dose escalation, but dose proportionality was not observed over the range of 150 to 450 mg. The values of t_{max} and $t_{1/2}$ were dose-independent. The mean $t_{1/2}$ of repirinast tablet was similar across all doses in the present study. The t_{max} of repirinast tablets was similar to values reported in previous studies (Beermann *et al.*, 1992; Schaefer *et al.*, 1993) and by the Romet® label. We report a mean $t_{1/2}$ that is comparable to the report by Schaefer, H.G (Schaefer *et al.*, 1993) and the Romet® label, but longer than the study of Beermann *et al.* (1992).

In this study, the 150 mg dose cohort after overnight fasting (5 males and 5 females), C_{max} and $AUC_{0-48\,h}$ of active metabolite MY-1250 were 308.9 ± 141.8 ng/mL and 937.0 ± 330.8 h·ng/mL. However, the Romet® label reported the C_{max} and AUC of 150 mg Romet® after overnight fasting (16 males) as 169 ± 27 ng/mL and 892 h·ng/mL. Beermann *et al.* (1992) reported the geometric mean C_{max} and AUC_{0-12}

$_{h}$ of 150 mg (12 males) as 138 ng/mL and 307 h·ng/mL. In this study, the C_{max} and $AUC_{0\text{-}48\,h}$ of active metabolite MY-1250 in the 300 mg dose and the 450 mg dose were 363.6 ± 149.2 ng/mL and 1492 ± 534 h·ng/mL, 441.7 ± 139.6 ng/mL and 1955 ± 902 h·ng/mL, respectively. Beermann *et al.* (1992) reported the geometric mean C_{max} and $AUC_{0\text{-}12}$ $_{h}$ of 300 mg dose and 450 mg dose as 191 ng/mL and 502 h·ng/mL, 241 ng/mL and 719 h·ng/mL, respectively. In this study, the mean clearance and volume of distribution of active metabolite MY-1250 was 164.4 ± 75.9 L/h and 3296 ± 2144 L, 202.2 ± 94.8 L/h and 4555 ± 2670 L, 237.5 ± 91.6 L/h and 5269 ± 3407 L in 150 mg, 300 mg and 450 mg dose, respectively. Beermann *et al.* (1992) reported the geometric mean clearance of active metabolite MY-1250 as 28.10 L/h, 26.4 L/h and 25.50 L/h in 150 mg, 300 mg and 450 mg dose, respectively. Schaefer *et al.* (1993) reported the mean clearance of active metabolite MY-1250 in a 300 mg dose as 14.88-18.18 L/h. The difference between the studies may be due to the differences in the formulation, release of the drug from the tablets tested, race, sample size, gender and subject variability.

In the multiple-dose study, ten subjects (5 males and 5 females) in group 2 received 150 mg repirinast tablets every 12 h for 5 days in the fasting state. There was no difference in $C_{min\text{-}ss}$ was found by ANOVA analysis. The t_{max} and $t_{1/2}$ showed no difference between the first and the last dose. The steady-state was achieved within 3 d after twice daily dosing of 150 mg repirinast tablets. There was no accumulation after repeated doses of 150 mg every 12 h for 5 days. The mean $t_{1/2}$ was similar to that of the single-dose study, indicating that the elimination rate of repirinast did not change during repeated administrations.

The safety evaluation during the study demonstrated that repirinast tablet was well tolerated in healthy Chinese volunteers over the studied dose range. The only major adverse event was elevated alanine aminotransferase (1/20, 5%), which was observed in one subject after administration of 150 mg repirinast tablets every 12 h for 5 days. This is a normal drug adverse reaction to repirinast and was likely related to the investigational drug. The reported AEs were mild and transient, and the subject recovered without any medication or further treatments.

CONCLUSIONS

This study demonstrated the single and multiple dose pharmacokinetics of repirinast tablet and its safety profile in healthy Chinese volunteers. Repirinast, as a prodrug, is immediately hydrolyzed to the active metabolite, MY-1250 (deesterified repirinast). The C_{max} and the AUC of MY-1250 increased with dose escalation, but dose proportionality was not observed over the range of 150 to 450 mg. The steady state was achieved within 3 days of twice daily dosing with the 150 mg repirinast tablet. There was no accumulation after multiple administrations. The repirinast tablet was well tolerated in healthy Chinese volunteers over the studied dose range.

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The authors have no conflicts of interest that are directly relevant to the content of this study.

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