The pharmacokinetics and bioavailability of rabeprazole following single intravenous infusion and oral administration in healthy Chinese volunteers

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Abstract

To investigate the pharmacokinetics and bioavailability of rabeprazole administrated by intravenous infusion and oral administration in healthy Chinese volunteers. A total of 20 male subjects were recruited and randomly assigned at the beginning of the study to receive a single dose of rabeprazole (20 mg) administrated either intravenously or orally. Following a 7-day washout period, all subjects received another 20 mg dose via the alternate route. Intravenous dose was given in constant infusion over 30 min, and the oral dose was given in two 10 mg tablets. Intravenous administration yielded the following measurements: the terminal half-life was (62.4±10.7) min; the C_{max} was (1308.6±266.4) ng·mL^{-1}; the total body clearance was (0.21±0.05) L·min^{-1}; the $AUC_{0-\tau}$ and $AUC_{0-\infty}$ were (99.6±21.9) mg·min·L^{-1} and (102.4±23.3) mg·min·L^{-1}, respectively. Oral administration yielded the following measurements: the half-life was (64.2±15.5) min; the C_{max} was (508.3±180.2) ng·ml^{-1}; Tmax was attained at about 229.5 min; the total body clearance was (0.31±0.10) L·min^{-1}; the $AUC_{0-\tau}$ and $AUC_{0-\infty}$ were (69.5±20.0) mg·min·L^{-1} and (70.6±20.2) mg·min·L^{-1}, respectively.

The bioavailability of rabeprazole was estimated to be 70.1% in healthy Chinese volunteers. The total body clearance after oral administration was significantly higher than that measured following intravenous administration (P<0.01).

Introduction

Proton pump inhibitors (PPIs) are the second most commonly prescribed drug class in the United States. They are the most effective drugs currently used for treatment of acid-related gastrointestinal disorders, such as gastroesophageal reflux disease (GERD), Barrett's esophagus, peptic ulcer disease (PUD), Zollinger-Ellison syndrome, gastrinomas, and esophagitis/gastritis.[1,2] PPIs act as largely displaced H_2 receptor antagonists, a property which contributes to their clinical efficacy, safety and relative lack of tachyphylaxis, as they are frequently prescribed both in the hospital and on an outpatient basis.[1]

Based on the mean 24-h gastric pH, the relative potencies of the five PPIs compared to omeprazole are 0.23, 0.90, 1.00, 1.60, and 1.82 for pantoprazole, lansoprazole, omeprazole, esomeprazole, and rabeprazole, respectively.[3] Rabeprazole has been shown to have a more rapid onset of proton pump (H^+, K^+-ATPase) inhibition, an increased potency in acid suppression, and some reversibility of its action when compared with omeprazole, lansoprazole and pantoprazole *in vitro* studies.[4,5] In patients with erosive oesophagitis and non-erosive reflux disease (NERD), rabeprazole has been shown to rapidly relieve symptoms, with significant improvement evident on the first day of treatment by orally.[6-8] Compared with healthy volunteers, patients with GERD require a 1.9-fold higher dose, and *Helicobacter pylori* (*H. pylori*) -positive individuals need only about 20% of the dose to achieve a given increase in mean 24-h intragastric pH.3 However, data from meta-analyses indicates little difference among cure rates of acid related diseases (i.e., GERD) at the approved doses of PPIs. Also *H. pylori* eradication rates did not differ very much among different PPIs, indicating a similar efficacy across different types of PPIs, ultimately reflecting differences in potency.[3]

The elimination of omeprazole, lansoprazole and pantoprazole involves hepatic oxidation mediated by Cytochrome P450 2C19 (CYP2C19) and CYP3A4.[9,10] The clearance of rabeprazole (RPZ) is largely nonenzymatic and less dependent on CYP2C19 and CYP3A4, because RPZ is relatively unstable compared with other PPIs and changes into its thioether form.[11,12] In terms of pharmacokinetics, usage of RPZ is more applicable across patients with different CYP450 genotypes.[13,14]

In healthy Caucasian and Hispanic subjects, mean bioavailability (F%) has been calculated to 52%.[15] Peak concentration (C_{max}) and AUC values were linearly related to the dose, whereas Tmax and half-life ($t_{1/2}$) were dose-independent. The extent of the pharmacokinetic parameters in Chinese following intravenous infusion compared to that of oral administration is not yet known. Therefore, the objective of the study was to investigate the bioavailability of rabeprazole in healthy Chinese volunteers.

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Materials and Methods

Design and demographic characteristics

The protocol was approved in advance by the hospital ethics committee (No.081404) and conducted in accordance with Good Clinical Practices and the Helsinki declaration. Subjects received oral and written explanations of the study and were given written informed consent prior to starting the study. All subjects (20 males) were randomized at the beginning of the study to receive either a single 20 mg dose of rabeprazole via either i.v. infusion or orally at 7:30 AM during Period 1. Following a 7-day washout period, each subject received the dose via the alternate route of administration during Period 2. None of the subjects consumed excessive amounts of alcohol or smoked, and none took or had taken any drugs during or for at least 1-week prior the study. Subjects were excluded based on clinically significant abnormal electrocardiogram, blood chemistry or urine analysis. The demographic characteristics of the subjects are presented in Table 1. The subjects were fasted from 10 h before to 4 h after RPZ administration. Water was not allowed for one hour prior to dosing and until one hour after dosing, except for the 250 mL of water administered with the study medication.

Rabeprazole sodium sterile injection powder (20 mg/ampoule) was provided by Nanjing Changao Pharmaceutical Science & Technology Company Limited, China.

Entericcoated tablets of rabeprazole (10 mg/tablet) were supplied by Eisai Company Limited, Japan. (Batch No: 070666). Rabeprazole sodium sterile injection powder was dissolved in sterile normal saline (100 mL), and was administered in a forearm vein via infusion over 30 minutes. The oral dose was administered as a single dose of two 10 mg enteric-coated tablets with 250 mL of water.

Sample collection and assays of rabeprazole

Peripheral blood samples were drawn from an i.v. cannula inserted into a forearm vein into 5-mL heparinized tubes immediately prior to and after the i.v. administration of rabeprazole at the following times: 5, 10, 20, 30, 40, 50, 70, 90, 120, 150, 210, 270, 330 min; Following the oral administration, blood samples were collected immediately prior to dosing and at 90, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540 and 600 min after the dose. After collection, the blood samples were immediately centrifuged at 3500 rpm for 10 min, and the plasma was separated and stored at -70°C until analysis.

RPZ plasma levels were measured by high-performance liquid chromatography (HPLC) with UV detection.[12] Ethyl hydroxybenzoate was used as internal marker for each sample (RPZ and ethyl hydroxybenzoate were supplied by the National Institute for the Control of Pharmaceutical and Biological Products, China). Briefly, the assay was performed according to the following procedure: 0.6 mL plasma was extracted with 4 mL of dichloromethane-isopropanol (90:10, v/v). The organic phase was transferred to a new tube and evaporated to dryness at 40°C. The residue was dissolved with 100 μL solution (0.1 mol·L^{-1} NaOH- acetonitrile, 75:25, v/v) and centrifuged at 15,000 rpm for 10 min, the supernatant was then filtered through a 0.45-μm filter, and prepared for analysis (LC-2010-CTH; Shimadzu, Japan) with a Kromasil 100-5C18 column (250 ×4.6 mm, 5 μm; EKA Chemicals, Sweden). The mobile phase consisted of phosphate buffer, acetonitrile (Merck, Germany) and methanol (Merck) (64: 31: 5 v/v/v; pH7.05). The flow rate was 1.2 mL/min, the detector wave was 290 nm, and the sample volume was 20 μL. The limit of quantification was 5 ng/mL, and the intra- and inter- batch relative standard deviations (RSD) were less than 7.6% and 11.0%, respectively.

Data and statistical analyses

The results are expressed as the mean ± SD. AUC, elimination half-life (t1/2), mean retention time (MRT), and total body clearance (Cltotal) were obtained by noncompartmental analysis, using a pharmacokinetic analysis package, DAS 2.0 (China). The bioavailability was calculated as the ratio of $AUC_{0-\tau}$ values following oral administration to $AUC_{0-\tau}$ values following intravenous infusion administration for each subject. The average bioavailability of rabepazole was estimated by the geometric mean of the individual value. Pharmacokinetic parameters were tested for statistical significance of sequence, period and treatment using analysis of variance (ANOVA) based on logarithmic transformed (natural log) AUCs and Cmax values. Statistical significance was set at $P<0.05$.

Results

The mean plasma level-time curve of rabeprazole is shown in Figure 1, and the pharmacokinetic parameters are presented in Table 2. The plasma concentration-time profile after intravenous administration was biphasic with a terminal half-life of (62.4±10.7) min. The individual plasma concentration-time curves after oral administration showed large interindividual variation. The Cmax was attained at about 229.5 min after oral administration, with a range of 150-360 min. The total body clearance after oral administration was significantly higher than that following intravenous administration. the bioavailability (F%) of rabeprazole was estimated to be 70.1%.

Discussion

In this study, the t1/2 after receiving a single i.v. or oral dose of rabeprazole was 62.4 min and 64.2 min, respectively; the Cl was 0.21 ml/min and 0.31 ml/min, respectively. While in Caucasian and Hispanic healthy male volunteers, the $t_{1/2}$ after receiving a single i.v. or oral dose has been reported to be 71.4 min and 91.8 min, respectively; and the Cl after receiving a single dose was 0.34 ml/min.[15] In Japanese healthy male volunteers, the $t_{1/2}$ after receiving a single oral dose has been reported to be 61.2 min.[16]

Intravenous infusion of 20 mg rabeprazole over 30 minutes resulted in a 2.6-fold increase in peak plasma concentrations and a more rapid elimination as compared to the same oral dose. The increased multiple of C_{max} was much lower than that of intravenous infusion over five minutes, which resulted in a 4-fold increase in peak plasma concentrations compared to the same oral dose.[15] Setoyama *et al*. reported that there was a significant difference between oral and intravenous eliminaion half-life, while in our study there was no significant difference between oral and intravenous eliminaion half-life.[15] The range of the half-life after oral administration was broad, probably due to the variability of dissolution of active ingredients from each of two enteric-coated tablets (each tablet contains 10 mg rabeprazole).

There was a significant difference between oral and intravenous total body clearance. The total body clearance after oral administration (0.31±0.10) L·min^{-1} was significantly higher than that following intravenous administration (0.21±0.05) L·min^{-1} ($P<0.01$). This could be due to a slower rate of absorption compared to

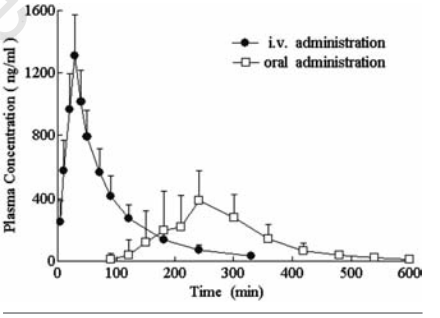

Figure 1. Mean plasma concentration-time curve of rabeprazole after single doses of 20 mg oral or intravenous administration. Each point represents the mean ± SD.

Table 1. Demographic characteristics of the subjects, with the values are given as the mean ± deviation (SD) with the range given in parenthesis.

Category	Results
Number of subjects	20
Sex	Male
Age (years)	26.7 3.2 (22-33)
Weight (kg)	67.7 6.0 (60-80)
Height (cm)	173.1 4.1 (168-183)
Body mass Index (Kg/m^2)	22.6 1.3 (20.3-23.9)

Table 2. The pharmacokinetics parameters of mean area under the plasma concentration-time curve, peak plasma level (C_{max}), half-life (t1/2), total body clearance (Cl/F) and MRT values after receiving a single intravenous or oral administration. The mean ± SD values are shown.

	C_{max} (ng·mL^{-1})	$t_{1/2z}$ (min)	Tmax (min)	Cl/F L ·min^{-1}	$MRT_{0-\tau}$ (min)	$AUC_{0-\tau}$ (mg·min·L^{-1})	$AUC_{0-\infty}$ (mg·min·L^{-1})	F (%)
p.o.	508.3±180.2	64.2±15.5	229.5±55.3	0.31±0.10	277.5±41.2	69.5±20.0	70.6±20.2	70.1±13.8
i.v. infusion	1308.6±266.4	62.4±10.7	30±0.5	0.21±0.05	80.1±8.1	99.6±21.9	102. 4±23. 3	

the rate of elimination.[15] The $MRT_{0-\tau}$ value after oral administration (277.5±41.2) min was significantly longer than that measured after intravenous administration (80.1±8.1) min ($P<0.01$). This also may be due to a slower rate of absorption compared to the rate of elimination.

RPZ transforms into the acid-activated form much faster than other PPIs, which further contributes to the inhibition of proton pumps immediately after RPZ reaches the target site. These properties make it feasible to lower the effective dose of RPZ to 10 mg/day, compared to the typical dosage of other PPIs, such as omeprazole (20 mg/day) and lansoprazole (30 mg/day).[17] Although PPIs have been very successful and effective, there are drawbacks such as incomplete acid suppression, high acidity at night, and requirement for mealtime dosing to ensure adequate levels of the drug during periods of pump activity.[18] The ubiquity of the various types of H^+, K^+-ATPase could also contribute to non-gastric effects. PPIs may also influence physiology in other ways, such as inducing transepithelial leak.[1]

In this study, intravenous infusion occured over 30 min, and the bioavailability was 70.1%. It is higher than the reported absolute bioavailability of 51.5% which was measured following an intravenous infusion time of 5 min.[15]

Only healthy young male subjects who were fasting had taken part in the study may be seen as a limitation. A further study including larger number of elder people (they are usually recommended to use rabeprazole) and patients, especially those with acid-related diseases, will be carried on to further evaluate the bioavailability of rabeprazole. Furthermore, the effect of food on the pharmacokinetic properties is also worthy carrying out.

Conclusions

The pharmacokinetics parameters of rabeprazole administrated by orally was significantly difference with those administrated by i.v. infusion. The total body clearance after oral administration was significantly higher than that measured following intravenous administration.

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